

4-AMINOPYRIMIDINES AS ADENOSINE RECEPTOR ANTAGONISTS

The present invention relates to new antagonists of adenosine receptors, in particular antagonist of the A_{2A} adenosine receptor subtype, the use of said compounds in the treatment of diseases, and disorders susceptible of being ameliorated by antagonism of adenosine receptors, in particular in the treatment of disorders of the central nervous which are known to be improved by the use of antagonists of the A_{2A} adenosine receptors, more specifically movement disorders such as Parkinson's disease, restless leg syndrome and dyskinesia and to pharmaceutical compositions comprising said compounds.

The effects of adenosine are mediated through at least four specific cell membrane receptors so far identified and classified as receptors A_1 , A_{2A} , A_{2B} and A_3 belonging to the G protein-coupled receptor family. The A_1 and A_3 receptors down-regulate cellular cAMP levels through their coupling to Gi proteins, which inhibit adenylate cyclase. In contrast, A_{2A} and A_{2B} receptors couple to Gs proteins that activate adenylate cyclase and increase intracellular levels of cAMP. Through these receptors, adenosine regulates a wide range of physiological functions.

Thus, in the cardiovascular system the activation of the A_1 receptor protects cardiac tissue from the effects of ischemia and hypoxia. A similar protective effect is also produced by antagonism of the A_{2A} receptor, which enhances A_1 -receptor-induced antiadrenergic responses and may also be useful in the treatment of acute myocardial ischemia and supraventricular arrhythmias (Norton GR et al. *Am J Physiol.* 1999; 276(2 Pt 2):H341-9; Auchampach JA, Bolli R. *Am J Physiol.* 1999; 276(3 Pt 2):H1113-6). In addition, the A_{2B} adenosine receptor subtype (Feoktistov, I. et al., *Pharmacol. Rev.* 1997, 49, 381-402) appears to be involved in the control of vascular tone and the regulation of vascular smooth muscle growth.

In the kidney, adenosine exerts a biphasic action, inducing vasodilation at high concentrations and vasoconstriction at low concentrations. Thus, adenosine plays a role in the pathogenesis of some forms of acute renal failure that may be ameliorated by A_1 receptor antagonists (Costello-Boerrigter LC, et al. *Med Clin North Am.* 2003 Mar; 87(2): 475-91; Gottlieb SS., *Drugs.* 2001; 61(10): 1387-93).

- Adenosine is also involved in the physiopathology of the immune system. It can induce degranulation of activated human mast cells through the A_{2B} and/or A_3 receptor. Thus A_{2B} and/or A_3 antagonists prevent mast cell degranulation and are, therefore, useful in the treatment, prevention or suppression of disease states induced by activation of the A_{2B} and/or A_3 receptor and mast cell degranulation. These disease states include but are not limited to asthma, myocardial reperfusion injury, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, other autoimmune diseases and inflammatory bowel diseases.
- 10 Furthermore, in the respiratory system adenosine induces bronchoconstriction, modulates airway inflammation and promotes neutrophil chemotaxis. Therefore, an adenosine antagonist would be particularly useful in the treatment of asthma.
- 15 In the gastrointestinal and metabolic system, the A_{2B} adenosine receptor subtype (Feoktistov, I. et al., *Pharmacol. Rev.* **1997**, 49, 381-402) seems to be involved in the regulation of hepatic glucose production, the modulation of intestinal tone, as well as intestinal secretion. Thus, A_{2B} antagonists may also be useful in the treatment of diabetes mellitus and obesity.
- 20 In the central nervous system adenosine is a potent endogenous neuromodulator, which controls the presynaptic release of many neurotransmitters and is thus involved in motor function, sleep, anxiety, pain and psychomotor activity. All adenosine receptor subtypes are present in the brain, with A_1 and A_{2A} subtypes being differentially distributed. The former are found predominantly in the hippocampus and cortex, whilst the latter are found
- 25 mainly in the striatum. Adenosine A_{2A} receptors modulate the release of GABA in the striatum, which possibly regulates the activity of medium spiny neurons.

Thus, A_{2A} receptor antagonists may be a useful treatment for neurodegenerative movement disorders such as Parkinson and Huntington's disease (Tuite P, et al., *J. Expert Opin Investig Drugs.* **2003**; 12: 1335-52; Popoli P. et al. *J Neurosci.* **2002**; 22:1967-75), dystonias such as restless leg syndrome (Happe S, et al., *Neuropsychobiology.* **2003**; 48: 82-6), and dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs (Jenner P. *J Neurol.* **2000**; 247 Suppl2: II43-50).

In the treatment of Parkinson's disease an A_{2A} antagonist may be useful not only as monotherapy, but also when administered in combination with L-DOPA and/or one or more of the following drugs: dopamine agonists, inhibitors of dopamine decarboxylase, catechol-O-methyltransferase inhibitors and inhibitors of monoamine oxidase.

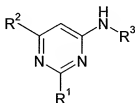
5

In addition, A_{2A} antagonists may have therapeutic potential as neuroprotectants (Stone TW. et al., *Drug. Dev. Res.* **2001**; 52: 323-330), and in the treatment of sleep disorders (Dunwiddie TV et al., *Ann. Rev. Neurosci.* **2001**; 24: 31-55).

- 10 It has now been found that certain 4-aminopyrimidine derivatives are novel potent antagonists the A_{2A} adenosine receptor and can therefore be used in the treatment or prevention of diseases susceptible to amelioration by antagonism of the adenosine receptor
- 15 Further objectives of the present invention are to provide a method for preparing said compounds; pharmaceutical compositions comprising an effective amount of said compounds; the use of the compounds in the manufacture of a medicament for the treatment of pathological conditions or diseases susceptible of being improved by antagonism of an adenosine receptor, in particular by antagonism of the A_{2A} adenosine
- 20 receptor ; methods of treatment of pathological conditions or diseases susceptible to amelioration by antagonism of an adenosine receptor, in particular by antagonism of the A_{2A} adenosine receptor comprising the administration of the compounds of the invention to a subject in need of treatment and combinations of said compounds with one or more of the following drugs: L-DOPA, dopamine agonists, inhibitors of dopamine decarboxylase,
- 25 catechol-O-methyltransferase inhibitors and inhibitors of monoamine oxidase.

Thus, the present invention is directed to new 4-aminopyrimidine derivatives of formula (I))

30



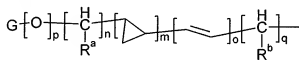
(I)

wherein

- R¹ and R² independently represent a monocyclic or polycyclic heteroaryl group optionally substituted by one or more substituents selected from the group consisting of halogen atoms, straight or branched, optionally substituted lower alkyl, cycloalkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, -SH, straight or branched optionally substituted lower alkylthio, cyano, -NR'R'', -CO₂R', wherein R' and R'' each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R'' together with the nitrogen atom to which they are attached form a cyclic group;
- 5 substituted lower alkylthio, cyano, -NR'R'', -CO₂R', wherein R' and R'' each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R'' together with the nitrogen atom to which they are attached form a cyclic group;
- 10 R³ represents a group selected from -COR⁴, -CON(R⁴)R⁵, -COOR⁴ and -R⁴

wherein R⁴ represents a group selected from:

- hydrogen atoms,
- 15 • a straight or branched lower alkyl group which is optionally substituted by one or more halogen atoms or by one or more cycloalkyl, hydroxy, lower alkoxy, lower alkylthio, amino, mono- or dialkylamino, alkoxyalkyl, hydroxycarbonyl, alkoxy carbonyl and nitrile groups;
- a group of formula:



20

wherein:

- m, o and p are independently 0 or 1;
- n and q are independently selected from integers from 0 to 6;
- R^a and R^b are independently a hydrogen atom or a lower alkyl group;
- 25 G is a group selected from cycloalkyl, aryl or heteroaryl groups which are optionally substituted by one or more halogen atoms or by one or more lower alkyl, cycloalkyl, lower haloalkyl, hydroxy, lower alkoxy, lower alkylthio, amino, mono- or dialkylamino, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxy carbonyl and nitrile groups;

30

and R⁵ represents a hydrogen atom or a lower alkyl, cycloalkyl or benzyl group; or

R⁴ and R⁵ together with the nitrogen atom to which they are attached form a saturated or unsaturated ring which is optionally substituted by one or more lower alkyl, cycloalkyl or benzyl groups;

- 5 or pharmaceutically acceptable salts thereof;

with the proviso that the compound is not 2,6-dipyridin-4-ylpyrimidin-4-amine.

- Other aspects of the present invention are: a) pharmaceutical compositions comprising an effective amount of said compounds, b) the use of said compounds in the manufacture of a medicament for the treatment of diseases susceptible of being improved by antagonism of an adenosine receptor, in particular by antagonism of the A_{2A} adenosine receptor; c) methods of treatment of diseases susceptible to amelioration by antagonism of an adenosine receptor, in particular by antagonism of the A_{2A} adenosine receptor, which
- 15 methods comprise the administration of the compounds of the invention to a subject in need of treatment and combinations of said compounds with one or more of the following drugs: L-DOPA, dopamine agonists, inhibitors of dopamine decarboxylase, catechol-O-methyltransferase inhibitors and inhibitors of monoamine oxidase.
- 20 As used herein the term lower alkyl embraces optionally substituted, linear or branched radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

- Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl and tert-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, isopentyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, n-hexyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl and iso-hexyl radicals.
- 25

- As used herein, the term lower alkoxy embraces optionally substituted, linear or branched oxy-containing radicals each having alkyl portions of 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.
- 30

- Preferred alkoxy radicals include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy, t-butoxy, trifluoromethoxy, difluoromethoxy, hydroxymethoxy, 2-hydroxyethoxy or
- 35 2-hydroxypropoxy.

As used herein, the term lower alkylthio embraces radicals containing an optionally substituted, linear or brached alkyl radicals of 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

5

Preferred optionally substituted alkylthio radicals include methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, sec-butylthio, t-butylthio, trifluoromethylthio, difluoromethylthio, hydroxymethylthio, 2-hydroxyethylthio or 2-hydroxypropylthio.

- 10 As used herein, the term cyclic group embraces, unless otherwise specified, carbocyclic and heterocyclic radicals. The cyclic radicals can contain one or more rings. Carbocyclic radicals may be aromatic or alicyclic, for example cycloalkyl radicals. Heterocyclic radicals also include heteroaryl radicals.

- 15 As used herein, the term aromatic group embraces typically a 5- to 14- membered aromatic ring system, such as a 5- or 6- membered ring which may contain one or more heteroatoms selected from O, S and N. When no heteroatoms are present the radical is named aryl radical and when at least one heteroatom is present it is named heteroaryl radical. The aromatic radical can be monocyclic or polycyclic, such as phenyl or naphthyl.
- 20 When an aromatic radical or moiety carries 2 or more substituents, the substituents may be the same or different.

As used herein, the term aryl radical embraces typically a C₆-C₁₄ monocyclic or polycyclic aryl radical such as phenyl or naphthyl, anthranyl or phenanthryl. Phenyl is preferred.

- 25 When an aryl radical carries 2 or more substituents, the substituents may be the same or different.

- As used herein, the term heteroaryl radical embraces typically a 5- to 14- membered ring system comprising at least one heteroaromatic ring and containing at least one
- 30 heteroatom selected from O, S and N. A heteroaryl radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom.

Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, oxadiazolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, thienyl, pyrrolyl, pyridinyl, benzothiazolyl, indolyl,

- 35 indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthridinyl, quinoxalinyl,

quinazoliny, quinoliziny, cinnoliny, triazolyl, indoliziny, indoliny, isoindoliny, isoindolyl, imidazolidiny, pteridiny and pyrazolyl radicals. Pyridyl, thienyl, furanyl, pyrazolyl, pyridaziny, pyrimidiny and quinolyl radicals are preferred.

- 5 When a heteroaryl radical carries 2 or more substituents, the substituents may be the same or different.

As used herein, some of the atoms, radicals, moieties, chains or cycles present in the general structures of the invention are "optionally substituted". This means that these

- 10 atoms, radicals, moieties, chains or cycles can be either unsubstituted or substituted in any position by one or more, for example 1, 2, 3 or 4, substituents, whereby the hydrogen atoms bound to the unsubstituted atoms, radicals, moieties, chains or cycles are replaced by chemically acceptable atoms, radicals, moieties, chains or cycles. When two or more substituents are present, each substituent may be the same or different.

15

As used herein, the term halogen atom embraces chlorine, fluorine, bromine or iodine atoms typically a fluorine, chlorine or bromine atom, most preferably chlorine or fluorine. The term halo when used as a prefix has the same meaning.

- 20 As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

- 30 Other preferred salts according to the invention are quaternary ammonium compounds wherein an equivalent of an anion (X^-) is associated with the positive charge of the N atom. X^- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an organic acid such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, trifluoroacetate, methanesulphonate and p-toluenesulphonate. X^- is preferably
- 35

an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate, succinate or trifluoroacetate. More preferably X- is chloride, bromide, trifluoroacetate or methanesulphonate.

- 5 As used herein, an N-oxide is formed from the tertiary basic amines or imines present in the molecule, using a convenient oxidising agent.

According to one embodiment of the present invention in the compounds of formula (I),
10 R¹ represents a monocyclic heteroaryl group selected from the group consisting of furyl, thienyl, thiazolyl, oxazolyl, pirazinyl, pirazolyl, piridaziny, imidazolyl, triazolyl, pirimidiny and pyridyl groups which groups are optionally substituted by one or more substituents selected from the group consisting of halogen atoms and straight or branched, optionally substituted lower alkyl.

15

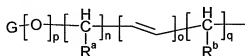
According to a preferred embodiment of the present invention in the compounds of formula (I), R¹ represents a monocyclic heteroaryl group selected from the group consisting of furyl, thienyl, pirazolyl, triazolyl, thiazolyl and pyridyl groups which groups are optionally substituted by one or more substituents selected from the group consisting of
20 halogen atoms and straight or branched, optionally substituted lower alkyl.

According to another embodiment of the present invention in the compounds of formula (I), R² represents a monocyclic heteroaryl group selected from the group consisting of pirazolyl, furyl, thiazolyl, oxazolyl, pyridyl, pirimidiny, pirazinyl, piridaziny, thienyl,
25 imidazolyl and triazolyl groups which groups are optionally substituted by one or more substituents selected from the group consisting of halogen atoms and straight or branched, optionally substituted lower alkyl.

According to another preferred embodiment of the present invention in the compounds of
30 formula (I), R² represents a monocyclic heteroaryl group selected from the group consisting of pirazolyl, furyl, thiazolyl, pyridyl, thienyl and triazolyl groups which groups are optionally substituted by one or more substituents selected from the group consisting of halogen atoms and straight or branched, optionally substituted lower alkyl.

According to still another embodiment of the present invention in the compounds of formula (I), R⁴ represents a group selected from:

- hydrogen atoms,
- 5 • a straight or branched lower alkyl group which is optionally substituted by one or more halogen atoms;
- a group of formula:



wherein:

- 10 o and p are independently 0 or 1;
- n and q are independently selected from integers from 0 to 6;
- R^a and R^b are independently a hydrogen atom or a lower alkyl group;
- G is a group selected from cycloalkyl, aryl or heteroaryl groups which are optionally substituted by one or more halogen atoms or by one or more lower
- 15 alkoxy groups;
- and R⁵ represents a hydrogen atom.

According to still another preferred embodiment of the present invention in the compounds of formula (I), R⁴ represents a group selected from:

- 20 • hydrogen atoms,
- a straight or branched lower alkyl group which is optionally substituted by one or more halogen atoms;
- a group selected from cycloalkylalkyl, phenylalkyl, heteroarylalkyl, phenoxyalkyl
- 25 and heteroaryloxyalkyl groups which groups are optionally substituted by one or more halogen atoms or by one or more lower alkoxy groups;
- and R⁵ represents a hydrogen atom.

- 30 According to still another preferred embodiment of the present invention in the compounds of formula (I), R¹ is a 2-furyl group and R² is a pirazolyl group which is optionally substituted by one or more lower alkyl groups.

Particular individual compounds of the invention include:

- 2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
 5 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]isobutyramide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]tertbutyramide
 Cyclopropanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide
 Cyclobutanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide
 Cyclohexanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide
 10 3-Cyclopentyl-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl] propionamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)-acetamide
 2-(3,4-Dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenyl-propionamide
 E-2-Phenylcyclopropanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl) pyrimidin-4-
 15 y]amide
 3,3,3-Trifluoro-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl] propionamide
 3-(3,4-Dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-methyl-3-phenylpropionamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenoxy-propionamide
 20 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)-propionamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl) acetamide
 E-3-(3,4-Dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acrylamide
 2-(Furan-2-yl)-6-(3,5-dimethylpyrazol-1-yl)pyrimidin-4-ylamine
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]acetamide
 25 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl] propionamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl] isobutyramide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl] tertbutyramide
 Cyclopropanecarboxylic acid [6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-
 y]amide
 30 3-Cyclopentyl-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-2-(4-
 methoxyphenyl)acetamide
 2-(3,4-Dimethoxyphenyl)-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-
 y]acetamide
 35 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenyl propionamide

- N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide
 3-(3,4-Dimethoxyphenyl)-*N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenoxy propionamide
- 5 *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)-pyrimidin-4-yl]-2-(pyridin-3-yl)acetamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)-pyrimidin-4-yl]-2-(pyridin-3-yl)propionamide
 2-(Furan-2-yl)-6-(4-methylpyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(Furan-2-yl)-6-(4-methylpyrazol-1-yl)-pyrimidin-4-yl] propionamide
 2-(Furan-2-yl)-6-(3-methylpyrazol-1-yl)pyrimidin-4-ylamine
- 10 *N*-[2-(Furan-2-yl)-6-(3-methylpyrazol-1-yl)-pyrimidin-4-yl] propionamide
 2-(Furan-2-yl)-6-(3- trifluoromethylpyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(Furan-2-yl)-6-(3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl] propionamide
 2-(Furan-2-yl)-6-(5-methyl-3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl amine
N-[2-(Furan-2-yl)-6-(5-methyl-3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl]propionamide
- 15 2-(Furan-2-yl)-6-[[1,2,4]triazol-1-yl]pyrimidin-4-ylamine
N-[2-(Furan-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]acetamide
N-[2-(Furan-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide
 3,3,3-Trifluoro-*N*-[2-(furan-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]-propionamide
 2-(5-Bromofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
- 20 *N*-[2-(5-Bromofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
 2-(5-Chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(5-Chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
 2-(5-Methylfuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(5-Methylfuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
- 25 *N*-[2-(Furan-2-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide
 2-(Furan-2-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]amide
 6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-ylamine
N-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]acetamide
N-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide
- 30 3-Cyclopentyl-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
 3-Phenyl-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
 3,3,3-Trifluoro-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
 3-(3,4-Dimethoxyphenyl)-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl) pyrimidin-4-yl]propionamide
 3-Phenoxy-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
- 35 *N*-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-2-(pyridin-3-yl) acetamide

- N-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-3-(pyridin-3-yl) propionamide
 E-3-(3,4-Dimethoxyphenyl)-N-[6-(pyrazol-1-yl)-2-(thiophen-2-yl) pyrimidin-4-yl]acrylamide
 6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-ylamine
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] acetamide
- 5 N-[6-(3,5-dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide
 2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine
 N-[2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]acetamide
 N-[2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide
- 10 3,3,3-Trifluoro-N-[2-(thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide
 N-[2-(3-Methylthiophen-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl] propionamide
 6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-ylamine
 N-[6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]acetamide
 N-[6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
- 15 3,3,3-Trifluoro-N-[6-(furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl] propionamide
 2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-ylamine
 N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-yl] propionamide
 N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide
- 20 6-(Furan-2-yl)-2-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine
 N-[6-(Furan-2-yl)-2-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide
 2-(Pyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-ylamine
 N-[2-(Pyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]propionamide
 2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-ylamine
- 25 N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl] propionamide
 N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide.
 2-(Pyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamine
 N-[2-(Pyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide
- 30 2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamine
 N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl] propionamide
 N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide
 2-(Pyrazol-1-yl)-6-(pyridin-4-yl)pyrimidin-4-ylamine
- 35 N-[2-(Pyrazol-1-yl)-6-(pyridin-4-yl)pyrimidin-4-yl]propionamide

- 6-(Furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-ylamine
 N-[6-(Furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-yl]propionamide
 2-(3-Methylpyridin-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
 N-[2-(3-methylpyridin-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
- 5 6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine
 N-[6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]acetamide
 N-[6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide
 6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl] acetamide
- 10 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl] propionamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide
 2-(Pyridin-3-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine
 3,3,3-Trifluoro-N-[2-(pyridin-3-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl] propionamide
 6-(Furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine
- 15 N-[6-(Furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide
 6-(3,5-dimethylpyrazol-1-yl)-2-(pyridin-4-yl)pyrimidin-4-ylamine
 6-(Furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-ylamine
 N-[6-(Furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide
- 20 6-(Furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-ylamine
 N-[6-(Furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-yl]propionamide
 2-(4-Fluorophenyl)-N-[6-(furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-yl] acetamide
 N-(Cyclopropylmethyl)-2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-amine
 (2R)-2-[[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]propan-1-ol
- 25 3-[[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]propan-1-ol
 N-[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]ethane-1,2-diamine
 2-(2-Furyl)-N-[2-(4-methoxyphenyl)ethyl]-6-(pyrazol-1-yl)pyrimidin-4-amine
 N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-amine
 2-(2-Furyl)-6-(pyrazol-1-yl)-N-[2-(pyridin-2-yl)ethyl]pyrimidin-4-amine
- 30 2-(2-Furyl)-6-(pyrazol-1-yl)-N-[2-(pyridin-3-yl)ethyl]pyrimidin-4-amine
 2-(2-Furyl)-N-(3-phenylpropyl)-6-(pyrazol-1-yl)pyrimidin-4-amine
 2-(2-Furyl)-N-[3-(imidazol-1-yl)propyl]-6-(pyrazol-1-yl)pyrimidin-4-amine
 N-(Cyclopropylmethyl)-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
 (2R)-2-[[6-(Pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amino]propan-1-ol
- 35 3-[[6-(Pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amino]propan-1-ol

- N-(2-Aminoethyl)-N-[6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amine
 N-[2-(4-Methoxyphenyl)ethyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
 N-[2-(3,4-Dimethoxyphenyl)ethyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
 6-(Pyrazol-1-yl)-N-[2-(pyridin-2-yl)ethyl]-2-(thien-2-yl)pyrimidin-4-amine
 5 6-(Pyrazol-1-yl)-N-[2-(pyridin-3-yl)ethyl]-2-(thien-2-yl)pyrimidin-4-amine
 N-(3-Phenylpropyl)-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
 N-[3-(Imidazol-1-yl)propyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
 Ethyl 6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-ylcarbamate
 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(2-phenyl-cyclopropyl)urea
 10 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-propylurea
 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-isopropylurea
 1-Cyclopentyl-3-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]urea
 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(4-methoxy-phenyl)urea
 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenethylurea
 15 1-Benzyl-3-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]urea

Of outstanding interest are:

- 2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
 20 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]tertbutylamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)-acetamide
 2-(3,4-Dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide
 3,3,3-Trifluoro-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
 25 . N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)-propionamide
 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)acetamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]tertbutylamide
 3-Cyclopentyl-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-2-(4-
 30 methoxyphenyl)acetamide
 2-(3,4-Dimethoxyphenyl)-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]acetamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenylpropionamide
 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-2-(pyridin-3-yl)acetamide
 35 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-2-(pyridin-3-yl)propionamide

2-(Furan-2-yl)-6-(3- trifluoromethylpyrazol-1-yl)pyrimidin-4-ylamine

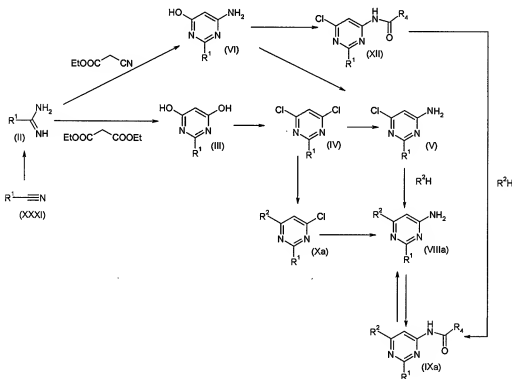
The compounds of the present invention may be prepared by one of the processes described below.

5

Compounds of formula (I) and in particular those of formulas (VIIIa) or (IXa) where R^1 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a nitrogen atom can be obtained as shown is Scheme 1.

10

Scheme 1



- 15 The carboxyamidines of formula (II), wherein R^1 is a monocyclic or polycyclic heteroaryl group linked to the carboxyamidine group through a carbon atom can be obtained by reacting a nitrile of formula (XXXI) with trimethylaluminum and ammonium chloride, in a solvent such as benzene, toluene or xylene, at a temperature from 80° to 120°. It also can be obtained by reaction of a nitrile of formula (XXXI) with sodium methoxide in methanol

at room temperature, followed by reaction with ammonium chloride at the same temperature.

- The carboxyamidines of formula (II) can be reacted with diethyl malonate in a solvent
- 5 such as methanol, ethanol, isopropyl alcohol, butyl alcohol or tetrahydrofuran, in the presence of a base, such as sodium methoxide, sodium ethoxide or potassium *tert*butoxide and at a temperature from room temperature to the boiling point of the solvent to yield the pyrimidine-4,6-diols of formula (III).
- 10 The resulting pyrimidine-4,6-diols of formula (III) can be reacted with a chlorinated agent such as phosphorus oxychloride, phosphorus pentachloride or a mixture of them, in a solvent such as phosphorus oxychloride, benzene or toluene, at a temperature from room temperature to the boiling point of the solvent to yield the 4,6-dichloropyrimidine compounds of formula (IV). Optionally, the presence of a base such as
- 15 dimethylaminoaniline, triethylamine or diisopropyl-ethylamine may be needed in this reaction step.

- The reaction of the 4,6-dichloropyrimidine compounds of formula (IV) with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at
- 20 a temperature from 80° to 140° produces the 6-chloropyrimidin-4-amines of formula (V).

- The resulting the 6-chloropyrimidin-4-amines of formula (V) are reacted with a compound of formula R^2-H wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the carboxyamidine group through a nitrogen atom to yield the compounds of formula (VIIIa)
- 25 which is a particular case of the compounds of formula (I) according to the invention. The reaction is carried out in a solvent such as dimethylformamide, dimethylacetamide or dimethylsulfoxide, in the presence of a base, such as sodium hydride, potassium carbonate or cesium carbonate, at a temperature from 60° to 140°C.
- 30 The compounds of formula (VIIIa) can be acylated by an acid chloride and a base, such as pyridine, triethylamine or diisopropylethylamine, in a solvent such as tetrahydrofuran, methylene chloride, chloroform or pyridine, at a temperature from room temperature to the boiling point of the solvent to yield the compounds of formula (IXa) which is a particular case of the compounds of formula (I) according to the invention. Compounds of formula

(IXa) can also be prepared by reaction of amine (VIIIa) with an anhydride, at a temperature from 80° to 160°C.

5 The 4,6-dichloropyrimidine compounds of formula (IV) can also be converted into the 4-chloropyrimidines of formula (Xa) by reaction with a compound of formula R^2-H wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the carboxyamidine group through a nitrogen atom. The reaction is carried out in a solvent such as dimethylformamide, dimethylacetamide or dimethylsulfoxide, in the presence of a base, such as sodium hydride, potassium carbonate or cesium carbonate, at a temperature from
10 60° to 140°C.

The resulting 4-chloropyrimidines of formula (Xa) can then be converted to the compounds of formula (VIIIa) according to the invention by reaction with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at
15 a temperature from 80°C to 140°C.

Alternatively, the compounds of formula (VIIIa) according to the invention can also be obtained from the compounds of formula (IXa) by reaction with a mineral acid, such as hydrochloric acid or sulphuric acid, in a solvent such as water, methanol, ethanol or
20 isopropyl alcohol, at a temperature from room temperature to the boiling point of the solvent.

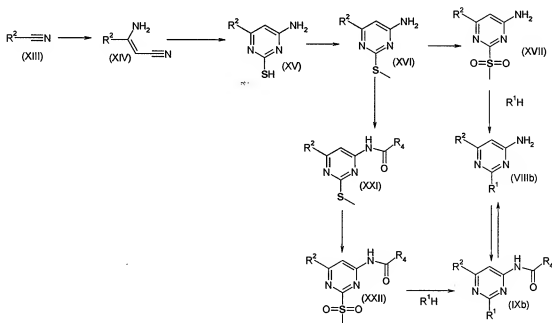
The compounds of formula (IXa) according to the invention can be obtained by reaction of the compounds of formula (XII) with compounds of formula R^2H wherein R^2 is as
25 hereinabove-defined. The reaction is carried out in a solvent such as dimethylformamide, dimethylacetamide or dimethylsulfoxide, in the presence of a base, such as sodium hydride, potassium carbonate or cesium carbonate, at a temperature from 60° to 140°C.

The compounds of formula (XII) can be obtained from the 6-aminopyrimidin-4-ol
30 compounds of formula (VI) by reaction with a carboxylic acid of formula R^4COOH , wherein R^4 is as hereinabove-defined in the presence of a chlorinated agent such as phosphorus oxychloride, phosphorus pentachloride or thionyl chloride, at a temperature from 60° to 120°C.

The 6-aminopyrimidin-4-ol compounds of formula (VI) are in turn obtained by reaction of the carboxyamidines of formula (II) with ethylcyanoacetate. The reaction is carried out in a solvent such as methanol, ethanol, isopropyl alcohol, butyl alcohol or tetrahydrofuran, in the presence of a base, such as sodium methoxide, sodium ethoxide or potassium *tert*butoxide and at a temperature from room temperature to the boiling point of the solvent.

Compounds of formula (I) and in particular those of formulas (VIIIb) or (IXb) where R¹ is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a nitrogen atom and R² is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom can be obtained as shown in Scheme 2.

Scheme 2



15

The aminonitriles of formula (XIV) can be obtained by reacting the nitriles of formula (XII) wherein R² is as hereinabove-defined and acetonitrile, in the presence of a base, preferably as lithium diisopropylamide or potassium *tert*butoxide, in a solvent such as benzene, toluene or xylene, at a temperature from room temperature to the boiling point of the solvent.

20

The resulting aminonitriles (XIV) are reacted with thiourea, in a solvent such as methanol, ethanol, isopropyl alcohol, butyl alcohol or tetrahydrofuran, in the presence of a base such as sodium methoxide, sodium ethoxide or potassium *tert*butoxide, at a temperature from 60° to 140°C to yield 4-aminopyrimidine-2-thiols of formula (XV).

5

The 4-aminopyrimidine-2-thiols of formula (XV) can be reacted in a solvent such as water, methanol, ethanol, dimethylformamide or dimethylsulfoxide, with methyl iodide or dimethylsulfate, in the presence of a base such as sodium hydroxide, sodium carbonate, potassium carbonate or sodium hydride, and a temperature from room temperature to 80°C to yield the 2-(methylthio)pyrimidin-4-amines of formula (XVI).

10

The 2-(methylthio)pyrimidin-4-amines of formula (XVI) can either be reacted with an oxidizing agent, preferably *m*-chloroperbenzoic acid, oxone or magnesium monoperoxyphthalate, in a solvent such as methanol, ethanol, acetone, methylene chloride or chloroform, and at a temperature from 0° to 70°C to yield 2-(methylsulfonyl)pyrimidin-4-amines of formula (XVII) or in the alternative they can be acylated by an acid chloride and a base, such as pyridine, triethylamine or diisopropylethylamine, in a solvent such as tetrahydrofuran, methylene chloride, chloroform or pyridine, at a temperature from room temperature to the boiling point of the solvent to yield the 2-(methylthio)pyrimidin-4-amides of formula (XXI).

20

The 2-(methylsulfonyl)pyrimidin-4-amines of formula (XVII) can be converted to the compounds (VIIIb) according to the present invention by reaction with compounds of formula R¹-H, wherein R¹ is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a nitrogen atom. The reaction is carried out in a solvent such as dimethylformamide, dimethylacetamide or dimethylsulfoxide, in the presence of a base, preferably sodium hydride, potassium carbonate or cesium carbonate, and at a temperature from 60° to 160°C. Similarly the 2-(methylsulfonyl)pyrimidin-4-amides of formula (XXII) can be converted to the compounds (IXb) according to the present invention following the same procedure.

30

The 2-(methylthio)pyrimidin-4-amides of formula (XXI) can be reacted with an oxidizing agent, preferably *m*-chloroperbenzoic acid, oxone or magnesium monoperoxyphthalate, in a solvent such as methanol, ethanol, acetone, methylene chloride or chloroform, and at a

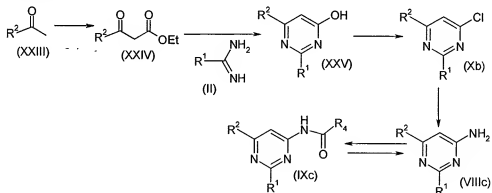
temperature from 0° to 70°C to yield the 2-(methylsulfonyl)pyrimidin-4-amides of formula (XXII).

Finally the compounds (VIIIb) according to the invention can be converted to the compounds (IXb) also according to the invention by reaction with an acid chloride and a base, such as pyridine, triethylamine or diisopropylethylamine, in a solvent such as tetrahydrofuran, methylene chloride, chloroform or pyridine, at a temperature from room temperature to the boiling point of the solvent. Compounds of formula (IXb) can also be prepared by reaction of amine (VIIIb) with an anhydride, at a temperature from 80° to 160°C.

The reverse operation through which compounds of formula (IXb) are converted into compounds of formula (VIIIb) is also possible and can be carried out by reaction with a mineral acid, such as hydrochloric acid or sulphuric acid, in a solvent such as water, methanol, ethanol or isopropyl alcohol, at a temperature from room temperature to the boiling point of the solvent.

Compounds of formula (I) and in particular those of formulas (VIIIc) or (IXc) where R¹ is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and R² is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom can be obtained as shown in Scheme 3.

Scheme 3



25

The reaction between methyl ketones of formula (XXIII), wherein R² is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and diethyl carbonate can be carried out in the presence of a base, preferably sodium hydride, in a

solvent such as benzene, toluene, ethyl ether, tetrahydrofuran or dioxane, and at a temperature from 40° to 120°C to yield the substituted ethyl 3-oxo-propanoates of formula (XXIV).

- 5 The pyrimidin-4-ol compounds of formula (XXV) can be obtained from the substituted ethyl 3-oxo-propanoates of formula (XXIV) by reaction with carboxyamidines of formula (II) in a solvent such as methanol, ethanol, isopropyl alcohol, butyl alcohol or tetrahydrofuran, in the presence of a base, such as sodium methoxide, sodium ethoxide or potassium *tert*butoxide and at a temperature from room temperature to the boiling point
10 of the solvent.

- The pyrimidin-4-ol compounds of formula (XXV) can be reacted with a chlorinated agent such as phosphorus oxychloride, phosphorus pentachloride or a mixture of them, in a solvent such as phosphorus oxychloride, benzene or toluene, at a temperature from room
15 temperature to the boiling point of the solvent to yield the 4-chloropyrimidines of formula (Xb). Optionally, the presence of a base such as dimethylaminoaniline, triethylamine or diisopropyl-ethylamine may be needed in this reaction step.

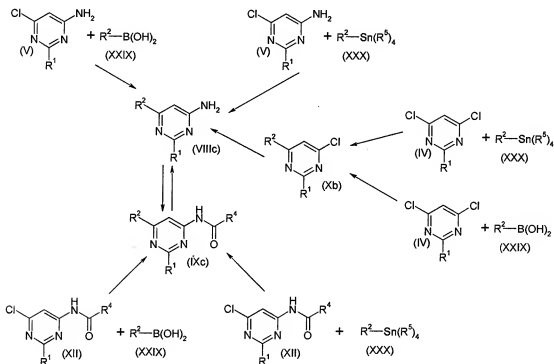
- The compounds of formula (VIIIc) according to the present invention can be prepared
20 from 4-chloropyrimidines of formula (Xb) by reaction with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at a temperature from 80°C to 140°C.

- Finally the compounds of formula (IXc) according to the present invention can be
25 prepared from the compounds of formula (VIIIc) by acylation with an acid chloride and a base, such as pyridine, triethylamine or diisopropylethylamine, in a solvent such as tetrahydrofuran, methylene chloride, chloroform or pyridine, at a temperature from room temperature to the boiling point of the solvent. Compounds of formula (IXc) can also be prepared by reaction of amine (VIIIc) with an anhydride, at a temperature from 80° to
30 160°C.

- Compounds of formula (VIIIc) can also be obtained from compounds of formula (IXc) by reaction with a mineral acid, such as hydrochloric acid or sulphuric acid, in a solvent such as water, methanol, ethanol or isopropyl alcohol, at a temperature from room temperature
35 to the boiling point of the solvent.

Compounds of formulae (VIIIc) and (IXc) where R^1 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom can also be obtained as shown is Scheme 4.

Scheme 4



10

The Suzuki reaction between the 4-aminopyrimidines of formulae (IV), (V) or (XII) and the boronic acid of formula (XXIX), wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom, is preferably carried out in an organic solvent such as methanol, ethanol, acetonitrile, dioxane, tetrahydrofuran, dimethoxyethane, benzene or toluene, optionally in the presence of water, at a temperature between 60° and 120°C, with a base such as sodium or potassium carbonate and a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0).

The Stille reaction between the 4-aminopyrimidines of formulae (IV), (V) or (XII) and the organotin derivative of formula (XXX), wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom, is preferably carried out in an

20

organic solvent such as methanol, ethanol, acetonitrile, dioxane, tetrahydrofuran, dimethoxyethane, benzene or toluene, optionally in the presence of water, at a temperature between 60° and 120°C, with a base such as sodium or potassium carbonate and a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0).

5

The 4-chloropyrimidine compounds of formula (Xb) can be converted to the compounds of formula (VIIIc) by reaction with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at a temperature from 80° to 140°C.

- 10 Finally the compounds of formula (IXc) according to the present invention can be prepared from the compounds of formula (VIIIc) by acylation with an acid chloride and a base, such as pyridine, triethylamine or diisopropylethylamine, in a solvent such as tetrahydrofuran, methylene chloride, chloroform or pyridine, at a temperature from room temperature to the boiling point of the solvent. Compounds of formula (IXd) can also be prepared by reaction of amine (VIIIc) with an anhydride, at a temperature from 80° to 160°C.

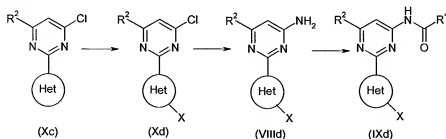
Compounds of formula (VIIIc) can also be obtained from compounds of formula (IXc) by reaction with a mineral acid, such as hydrochloric acid or sulphuric acid, in a solvent such as water, methanol, ethanol or isopropyl alcohol, at a temperature from room temperature to the boiling point of the solvent.

20

Compounds of formulae (VIIId) and (IXd) where R¹ is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and R² is a substituted heterocyclic group can be obtained as shown in Scheme 5.

25

Scheme 5



The substituted 4-chloro-2-(2-heteroaryl)pyrimidines of formula (Xd) can be obtained by reaction of the corresponding unsubstituted 4-chloro-2-(2-heteroaryl)pyrimidines of formula (Xc). When the heteroaryl group is a furyl group the reaction is preferably carried out with *N*-chlorosuccinimide ($X = \text{chloro}$) or *N*-bromosuccinimide ($X = \text{bromo}$), with a solvent such as dimethylformamide or dimethylsulfoxide, at a temperature from 40° to 100°C. Alternatively halogenating agent can be selected from the group consisting of Cl_2 , Br_2 , SOCl_2 and SOBr_2 .

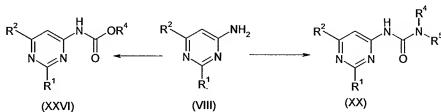
The 4-chloropyrimidine compounds of formula (Xd) can then be converted to the compounds of formula (VIIId) by reaction with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at a temperature from 80° to 140°C.

Finally the compounds of formula (IXd) according to the present invention can be prepared from the compounds of formula (VIIId) by acylation with an acid chloride and a base, such as pyridine, triethylamine or diisopropylethylamine, in a solvent such as tetrahydrofuran, methylene chloride, chloroform or pyridine, at a temperature from room temperature to the boiling point of the solvent. Compounds of formula (IXd) can also be prepared by reaction of amine (VIIId) with an anhydride, at a temperature from 80° to 160°C.

Compounds of formula (VIIId) can also be obtained from compounds of formula (IXd) by reaction with a mineral acid, such as hydrochloric acid or sulphuric acid, in a solvent such as water, methanol, ethanol or isopropyl alcohol, at a temperature from room temperature to the boiling point of the solvent.

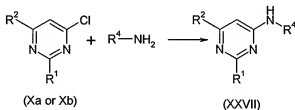
Carbamates of formula (XXVI), and ureas of formula (XX) can be synthesised as it is summarised on Scheme 6

30 Scheme 6



- The carbamates of formula (XXVI) are obtained by reaction of a compound of formula (VIII) with a compound of formula $Z\text{-COOR}^4$, wherein Z represents a leaving group such as halogen atom, preferably chlorine or a group selected from ethoxy, methoxy, p-nitrophenoxy and imidazolyl. The reaction is carried out in a solvent, such as tetrahydrofuran, chloroform, methylene chloride or dimethylformamide, in the presence of a base, preferably triethylamine, diisopropylethylamine, potassium carbonate or sodium hydroxide, at a temperature from -70° to 100°C .
- 10 The compounds of formula (VIII) can also be converted to the ureas of formula (XX) wherein R^5 is a hydrogen atom by reaction with an isocyanate of formula $R^4\text{-N=C=O}$ in a solvent such as benzene, toluene or xylene, at a temperature from room temperature to 140°C .
- 15 The synthesis of amines of formula (XXVII) can be prepared following Scheme 7

Scheme 7



- 20 When R^1 represents a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom, the compounds of formula (XXVII) can be obtained from the compounds of formulae (Xa and Xb) by reaction with an amine of formula $R^4\text{NH}_2$. The reaction is carried out in a solvent such as methanol, ethanol, isopropanol, butanol, pentanol, tetrahydrofuran or dimethylformamide, in the presence of a base such as an excess of the reacting amine $R^4\text{NH}_2$ or potassium carbonate, sodium carbonate, triethylamine or diisopropylethylamine, and at a temperature between room temperature and the boiling point of the solvent.
- 25
- 30 When the defined groups R^1 to R^5 are susceptible to chemical reaction under the conditions of the hereinbefore described processes or are incompatible with said

processes, conventional protecting groups may be used in accordance with standard practice, for example see T. W. Greene and P. G. M. Wuts in 'Protective Groups in Organic Chemistry', 3rd Edition, John Wiley & Sons (1999). It may be that deprotection will form the last step in the synthesis of compounds of formula (I).

5

The compounds of formulae (XIII), (XXIII), (XXIX), (XXX) and (XXXI), are known compounds or can be prepared by analogy with known methods.

10 In particular compounds of formulae (XXIX) and (XXXI) can be prepared by the methods described in Tyrrell, E.; Brookes, P; Synthesis, 2003, 4, 469-483; Condret, C. Synthetic Communications 1996, 26(19), 3543-3547 and Handbook of Organopalladium Chemistry for Organic Synthesis, Two Volume Set Edited by Ei-ichi Negishi. John Wiley and Sons, 2002.

15 PHARMACOLOGICAL ACTIVITY

Adenosine 2A receptor subtype competition radioligand binding assay

20 Human membranes from recombinant A2a receptors were purchased from Receptor Biology, Inc. (USA)

25 Competition assays were carried out by incubation of membranes from hA2a receptors transfected to HEK293 cells, [³H]ZM241385 as radioligand, buffer (50mM Tris-HCl (pH=7.4), 10mM MgCl₂, 1mM EDTA, 2 units/ml adenosine deaminase), and unlabelled ligand in a total volume of 0.2 ml for 90 min at 25°C. NECA was used to determinate non-specific binding. Filter over Schleicher&Schuell GF/52 filters (pre-soaked 0.5% polyethylenimine) in a Brandel cell harvester. Unbound radioligand was removed with 3x3 ml ice-cold 50mM Tris-HCl (pH=7.4), 0.9% NaCl.

30

Results are shown in Table 1

Table 1

Example	hA2a, IC50 (nM)
1	57
2	9

3	4.9
4	2.1
5	58
6	2.9
7	3.5
8	7.8
9	16.4
10	27
11	8
12	14.3
13	90.4
14	9.6
15	38.8
16	30.6
17	9.3
18	22.2
19	6
20	15.6
21	115.8
22	12.7
23	15.5
24	3.5
25	95
26	5.7
27	65.8
28	30
29	30
30	74.2
31	14.9
32	41.1
33	37.9
34	4.1
35	19

36	91.9
37	9.6
38	54.1
39	5.2
40	101
41	69.3
42	289.7
43	38.3
45	88.7
46	29.6
47	86.8
49	61.7
53	13.1
54	29.2
57	9.9
58	27.6
61	122
64	32.4
67	95
68	51
69	107
78	183.3
81	124
86	109.8
88	107
89	76
91	182.4
94	65
98	214.4
100	54.7
112	207
118	57.3
119	108

124	188
125	241
126	156

It can be seen from Table 1 that the compounds of formula (I) are potent inhibitors of the A_{2A} adenosine receptor subtype and selective over the other adenosine receptor subtypes.

5

The pyrimidin-4-amine derivatives of the invention are useful in the treatment or prevention of diseases known to be susceptible to improvement by treatment with an antagonist of an adenosine receptor, in particular those susceptible to improvement by treatment with an antagonist of the A_{2A} adenosine receptor. Such diseases are, for example ischemia, supraventricular arrhythmias, acute renal failure, myocardial reperfusion injury, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, other autoimmune diseases, inflammatory bowel diseases, asthma, diabetes mellitus, obesity, Parkinson disease, Huntington's disease, dystonias such as restless leg syndrome, dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs or sleep disorders.

10

15

Accordingly, the pyrimidin-4-amine derivatives of the invention and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compound and/or salts thereof, may be used in a method of treatment of disorders of the human body which comprises administering to a subject requiring such treatment an effective amount of pyrimidin-4-amine derivative of the invention or a pharmaceutically acceptable salt thereof.

20

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a pyrimidin-4-amine derivative of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, nasal, rectal, percutaneous or injectable administration.

25

30

The pharmaceutically acceptable excipients which are admixed with the active compound, or salts of such compound, to form the compositions of this invention are well-known *per se* and the actual excipients used depend *inter alia* on the intended method of administering the compositions.

5

Compositions of this invention are preferably adapted for injectable and *per os* administration. In this case, the compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules, inhalation aerosols, inhalation solutions, dry powder inhalation, or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

15 The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 2 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

20 The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

25 Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid.

30 Effective doses are normally in the range of 2-2000 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as a limiting.

35

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples (1 to 118) including the preparation of intermediates 1 to 52 which do not limit the scope of the invention in any way.

5 **General.** Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. Concentration refers to evaporation under vacuum using a Büchi rotatory evaporator. Reaction products were purified, when necessary, by flash chromatography on silica gel (40-63 μ m) with the solvent system indicated. Spectroscopic data were recorded on a Varian Gemini 200 spectrometer, Varian Gemini 300
10 spectrometer, Varian Inova 400 spectrometer and Bruker DPX-250 spectrometer. Melting points were recorded on a Büchi 535 apparatus. HPLC-MS were performed on a Gilson instrument equipped with a Gilson piston pump 321, a Gilson 864 vacuum degasser, a Gilson liquid handler 215, a Gilson 189 injection module, a Gilson Valvemat 7000, a 1/1000 splitter, a Gilson 307 make-up pump, a Gilson 170 diode array detector,
15 and a Thermoquest Finnigan aQa detector. Semi-preparative purifications were carried out using a Symmetry C18 reverse phase column (100 Δ , 5 μ m, 19 x 100 mm, purchased from WATERS), and water/ammonium formate (0,1%, pH=3) and acetonitrile/ammonium formate (0,1%, pH=3) as mobile phase.

20 **Intermediate 1. Furan-2-carboxamidine (HCl)**

To a solution of sodium methoxide (5.55 mmol) in methanol (50 mL) was added 2-furonitrile (5.0 g; 53.2 mmol). The mixture was stirred at room temperature for 3 hours. To the resulting solution was slowly added ammonium chloride (3.14 g, 58.7 mmol) and the mixture was stirred at room temperature for 68 hours. The resulting suspension was
25 filtered and the solvent removed under reduced pressure. The solid obtained was washed with ethyl ether (3x25 mL) to give 7.5 g (96.2%) of furan-2-carboxamidine (HCl).

δ (200 MHz, DMSO): 6.88-6.86 (m, 1H); 7.89 (d, J =3.8 Hz, 1H); 8.19 (s, 1H); 9.22 (s, 3H).

30 **Intermediate 2. 2-(Furan-2-yl)pyrimidine-4,6-diol**

To a solution of sodium ethoxide (0.191 mol) in ethanol (90 mL) was slowly added Intermediate 1 (5.6 g; 38.2 mmol). The mixture was stirred at room temperature for 30 minutes and then, diethyl malonate (4.87 g, 30.4 mmol) was added. The suspension was refluxed for 32 hours. The solvent was removed under reduced pressure, the residue was
35 suspended in water (100 mL) and acidified to pH=6 with 5N HCl. The resulting solid was

filtered and washed with water (50 mL), ethanol/ethyl ether (4:1, 25 mL), ethyl ether (2x25 mL). 2-(Furan-2-yl)pyrimidine-4,6-diol was obtained (4.2 g, 78%) as a pale yellow solid.

δ (300 MHz, DMSO): 5.00 (s, 1H); 6.60-6.70 (m, 1H); 7.40 (d, $J=3.4$ Hz, 1H); 7.80 (s, 1H).

Intermediate 3. 4,6-Dichloro-2-(furan-2-yl)pyrimidine

A suspension of Intermediate 2 (3.0 g; 16.8 mmol) and *N,N*-diisopropylethylamine (3.85 g; 29.8 mmol) in phosphorous oxychloride (17 mL) was refluxed for 3 hours. The solvent was removed under pressure and methylene chloride (50 mL) and ice were slowly added.

The organic phase was decanted and washed with water (2x25 mL), saturated solution of sodium bicarbonate (2x25 mL), brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give 4,6-dichloro-2-(furan-2-yl)pyrimidine (3.15 g, 87%) as a grey solid.

δ (300 MHz, CDCl_3): 6.63-6.61 (m, 1H); 7.22 (s, 1H); 7.46 (d, $J=3.4$ Hz, 1H); 7.68 (s, 1H).

Intermediate 4. 6-Chloro-2-(furan-2-yl)pyrimidin-4-ylamine

A suspension of Intermediate 3 (2.0 g; 9.3 mmol) in methanol (14 mL) and 30% ammonium hydroxide (27 mL) was heated in a pressure reactor for 20 hours. The solvent was partially removed under reduced pressure. The resulting solid was filtered, washed with water (25 mL), ethyl ether (25 mL), and dried. 6-Chloro-2-(furan-2-yl)pyrimidin-4-ylamine was obtained (1.48 g, 76%) as an off-white solid.

δ (400 MHz, CDCl_3): 5.21 (bs, 2H); 6.31 (s, 1H); 6.54 (m, 1H); 7.28 (d, $J=3.7$ Hz, 1H); 7.58 (s, 1H).

EXAMPLE 1. 2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine



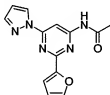
To a solution of Intermediate 4 (1.0 g; 5.1 mmol) in anhydrous DMF (20 mL) was added pyrazol (0.7 g; 10.2 mmol) and cesium carbonate (3.34 g; 10.2 mmol). The mixture was heated at 85°C for 21 hours. The solution was poured into water (50 mL) and extracted with ethyl acetate (2x25 mL). The organic phase was washed with water (2x25 mL) and

brine (25 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. The resulting solid was purified by column chromatography with silica gel, eluting with methylene chloride/methanol (3%), to give 2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine (0.64 g, 55%) as an off-white solid.

- 5 δ (250 MHz, CDCl₃): 5.12 (bs, 2H); 6.48-6.46 (m, 1H); 6.57-6.55 (m, 1H); 6.90 (s, 1H); 7.31 (d, J=3.6 Hz, 1H); 7.61 (s, 1H); 7.75 (d, J=1.2 Hz, 1H); 8.63 (d, J=3.0 Hz, 1H).

EXAMPLE 2. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide

10



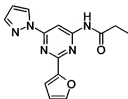
- To a solution of the title compound of Example 1 (0.30 g; 1.32 mmol) in methylene chloride (7 mL) was added pyridine (0.21 g; 2.64 mmol) and acetyl chloride (0.21 g; 2.64 mmol). The mixture was stirred at room temperature for 5 hours and pyridine (52 mg; 0.66 mmol) and acetyl chloride (52 mg; 0.66 mmol) were added. The reaction was allowed to stand for 1.5 further hours at room temperature. The solution was diluted with methylene chloride (20 mL), washed with 10% sodium hydroxide (2x10mL), brine (10mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure. Purification by column chromatography with silica gel, eluting with ethyl acetate/n-hexane (1:3), gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide (0.33 g, 92%) as an off-white solid.

- 20 δ (250 MHz, CDCl₃): 2.25 (s, 3H); 6.51-6.49 (m, 1H); 6.61-6.58 (m, 1H); 7.36-7.34 (m, 1H); 7.62 (s, 1H); 7.81 (s, 1H); 8.21 (bs, 1H); 8.54 (s, 1H); 8.65-8.63 (m, 1H).

25

EXAMPLE 3. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide

30

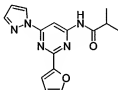


- Obtained from the title compound of Example 1 (0.34 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (0.35 g, 83%) as an off-white solid.

35

δ (250 MHz, CDCl_3): 1.28 (t, $J=7.3$ Hz, 3H); 2.48 (q, $J=7.3$ Hz, 2H); 6.50-6.48 (m, 1H); 6.60-6.58 (m, 1H); 7.34 (d, $J=3.6$ Hz, 1H); 7.62 (s, 1H); 7.79 (s, 1H); 8.13 (bs, 1H); 8.58 (s, 1H); 8.62 (d, $J=2.4$ Hz, 1H).

5 **EXAMPLE 4. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]isobutyramide**



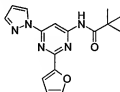
10

Obtained from the title compound of Example 1 (0.10 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]isobutyramide (90 mg, 72%) as an off-white solid.

15 δ (250 MHz, CDCl_3): 1.28 (d, $J=7.0$ Hz, 6H); 2.58 (h, $J=7.0$ Hz, 1H); 6.49 (dd, $J_1=2.7$ Hz, $J_2=1.5$ Hz, 1H); 6.60 (dd, $J_1=3.3$ Hz, $J_2=1.5$ Hz, 1H); 7.36 (dd, $J_1=3.6$ Hz, $J_2=0.9$ Hz, 1H); 7.65-7.63 (m, 1H); 7.80-7.78 (m, 1H); 8.08 (bs, 1H); 8.64-8.61 (m, 2H).

EXAMPLE 5. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]tertbutyramide

20

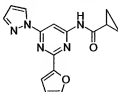


25 Obtained from the title compound of Example 1 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (from 10:90 to 15:85) as eluent gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]tertbutyramide (25 mg, 6%) as an off-white solid.

30 δ (250 MHz, CDCl_3): 1.35 (s, 9H); 6.49-6.47 (m, 1H); 6.59 (dd, $J_1=3.4$ Hz, $J_2=1.8$ Hz, 1H); 7.36-7.35 (m, 1H); 7.64-7.63 (m, 1H); 7.78-7.77 (m, 1H); 8.19 (bs, 1H); 8.62 (d, $J=2.7$ Hz, 1H); 8.66 (s, 1H).

EXAMPLE 6. Cyclopropanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide

35

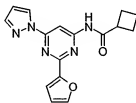


Obtained from the title compound of Example 1 (0.20 g) by the procedure described in
5 Example 2. Purification by column chromatography with silica gel and methylene
chloride/methanol (2%) as eluent gave cyclopropanecarboxylic acid [2-(furan-2-yl)-6-
(pyrazol-1-yl)pyrimidin-4-yl]amide (0.10 g, 39%) as an off-white solid.

δ (250 MHz, CDCl_3): 0.98-0.91 (m, 2H); 1.20-1.13 (m, 2H); 1.59-1.51 (m, 1H); 6.49 (dd, $J_1=2.7$ Hz, $J_2=1.5$ Hz, 1H); 6.59 (dd, $J_1=3.6$ Hz, $J_2=1.8$ Hz, 1H); 7.35 (d, $J=3.6$ Hz, 1H);
10 7.64-7.63 (m, 1H); 7.77 (d, $J=1.5$ Hz, 1H); 8.42 (bs, 1H); 8.56 (s, 1H); 8.62 (d, $J=2.7$ Hz, 1H).

EXAMPLE 7. Cyclobutanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide

15

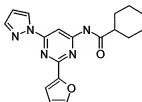


Obtained from the title compound of Example 1 (0.15 g) by the procedure described in
20 Example 2. Purification by column chromatography with silica gel and methylene
chloride/methanol (0.5%) as eluent gave cyclobutanecarboxylic acid [2-(furan-2-yl)-6-
(pyrazol-1-yl)pyrimidin-4-yl]amide (0.14 g, 67%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.50-1.93 (m, 6H); 3.22 (q, $J=8.5$ Hz, 1H); 6.49 (dd, $J_1=2.7$ Hz, $J_2=1.8$ Hz, 1H); 6.59 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 7.35 (d, $J=3.3$ Hz, 1H); 7.63 (m,
25 1H); 7.79 (m, 1H); 7.97 (bs, 1H); 8.62 (s, 1H); 8.63 (s, 1H).

EXAMPLE 8. Cyclohexanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide

30

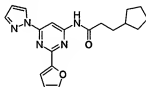


Obtained from the title compound of Example 1 (0.15 g) by the procedure described in
Example 2. Purification by column chromatography with silica gel and methylene

chloride/methanol (0.5%) as eluent gave cyclohexanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide (0.20 g, 91%) as an off-white solid.

δ (250 MHz, CDCl₃): 2.00-1.26 (m, 10H); 2.35-2.23 (m, 1H); 6.49 (dd, *J*₁=2.7 Hz, *J*₂=1.5 Hz, 1H); 6.59 (dd, *J*₁=3.3 Hz, *J*₂=1.8 Hz, 1H); 7.34 (dd, *J*₁=3.3 Hz, *J*₂=0.9 Hz, 1H); 7.63-7.62 (m, 1H); 7.78 (m, 1H); 8.14 (bs, 1H); 8.63-8.59 (m, 2H).

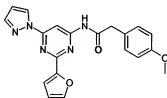
EXAMPLE 9. 3-Cyclopentyl-*N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide



Obtained from the title compound of Example 1 (0.20 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (from 10:90 to 20:80) as eluent gave 3-cyclopentyl-*N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (0.29 g, 94%) as an off-white solid.

δ (250 MHz, CDCl₃): 1.18-1.07 (m, 2H); 1.86-1.51 (m, 9H); 2.43 (t, *J*=7.4 Hz, 2H); 6.49 (dd, *J*₁=2.7 Hz, *J*₂=1.5 Hz, 1H); 6.59 (dd, *J*₁=3.3 Hz, *J*₂=1.5 Hz, 1H); 7.34 (dd, *J*₁=3.3 Hz, *J*₂=0.6 Hz, 1H); 7.63-7.62 (m, 1H); 7.80-7.79 (m, 1H); 8.16 (bs, 1H); 8.58 (s, 1H); 8.63 (dd, *J*₁=2.7 Hz, *J*₂=0.6 Hz, 1H).

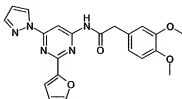
EXAMPLE 10. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide



Obtained from the title compound of Example 1 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:4) as eluent gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide (63 mg, 27%) as an off-white solid.

δ (250 MHz, CDCl₃): 3.73 (s, 2H); 3.82 (s, 3H); 6.50-6.48 (m, 1H); 6.58-6.56 (m, 1H); 6.91 (s, 1H); 6.94 (s, 1H); 7.32-7.23 (m, 3H); 7.61-7.60 (m, 1H); 7.80-7.79 (m, 1H); 8.06 (bs, 1H); 8.59 (s, 1H); 8.62 (d, *J*=2.7 Hz, 1H).

EXAMPLE 11. 2-(3,4-Dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide



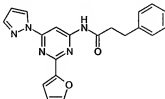
5

Obtained from the title compound of Example 1 (80 mg) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (0.5%) as eluent gave 2-(3,4-dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide (87 mg, 61%) as an off-white solid.

δ (250 MHz, CDCl_3): 3.73 (s, 2H); 3.90 (s, 6H); 6.51-6.48 (m, 1H); 6.59-6.56 (m, 1H); 6.84 (s, 1H); 6.88 (s, 2H); 7.33 (d, $J=3.3$ Hz, 1H); 7.61 (s, 1H); 7.80 (s, 1H); 8.10 (bs, 1H); 8.59 (s, 1H); 8.63 (d, $J=2.7$ Hz, 1H).

15

EXAMPLE 12. N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenylpropionamide

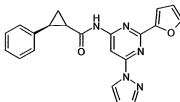


20

Obtained from the title compound of Example 1 (0.20 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:4) as eluent gave N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenylpropionamide (0.27 g, 85%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.74 (t, $J=7.8$ Hz, 2H); 3.08 (t, $J=7.8$ Hz, 2H); 6.51-6.49 (m, 1H); 6.60-6.57 (m, 1H); 7.35-7.22 (m, 6H); 7.62 (s, 1H); 7.81 (s, 1H); 8.11 (bs, 1H); 8.58 (s, 1H); 8.64 (m, 1H).

EXAMPLE 13. E-2-Phenylcyclopropanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide

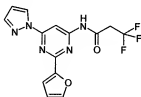


35

Obtained from the title compound of Example 1 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (0.5%) as eluent gave *E*-2-phenylcyclopropanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide (0.23 g, 95%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.49-1.40 (m, 1H); 1.86-1.75 (m, 2H); 2.71-2.63 (m, 1H); 6.50-6.49 (m, 1H); 6.57 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 7.14-7.11 (m, 2H); 7.34-7.19 (m, 4H); 7.61 (m, 1H); 7.79 (m, 1H); 8.59-8.58 (m, 2H); 8.63 (d, $J=2.7$ Hz, 1H).

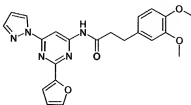
EXAMPLE 14. 3,3,3-Trifluoro-*N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide



To a solution of 3,3,3-trifluoropropionic acid (0.21 g; 1.65 mmol) in methylene chloride (4 mL) was added oxalyl chloride (0.21 g; 1.65 mmol) and a catalytic amount of DMF. The mixture was stirred at room temperature for 1 hour. This solution was cooled at 0°C and added at the same temperature to a solution of the title compound of Example 1 (125 mg; 0.55 mmol) and pyridine (123 mg; 1.65 mmol) in methylene chloride (4 mL). The mixture was stirred at room temperature for 22 hours and diluted with methylene chloride (8 mL). The organic phase was washed with water (2x8 mL) and brine (8 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. Purification by column chromatography with silica gel, eluting with ethyl acetate/*n*-hexane (1:4), gave 3,3,3-trifluoro-*N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (0.16 g, 87%) as an off-white solid.

δ (250 MHz, CDCl_3): 3.33 (q, $J=10.0$ Hz, 2H); 6.52-6.50 (m, 1H); 6.61-6.59 (m, 1H); 7.36 (d, $J=3.6$ Hz, 1H); 7.64-7.63 (m, 1H); 7.82-7.81 (m, 1H); 8.40 (bs, 1H); 8.54 (s, 1H); 8.65-8.63 (m, 1H).

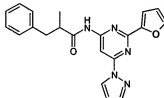
EXAMPLE 15. 3-(3,4-Dimethoxyphenyl)-*N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide



Obtained from the title compound of Example 1 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (from 30:70 to 40:60) as eluent gave 3-(3,4-dimethoxyphenyl)-*N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (0.27 g, 72%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.71 (t, $J=7.6$ Hz, 2H); 3.02 (t, $J=7.6$ Hz, 2H); 3.85 (s, 3H); 3.86 (s, 3H); 6.50 (dd, $J_1=2.7$ Hz, $J_2=1.5$ Hz, 1H); 6.59 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 6.80-6.76 (m, 3H); 7.34 (dd, $J_1=3.3$ Hz, $J_2=0.9$ Hz, 1H); 7.62 (dd, $J_1=1.8$ Hz, $J_2=0.9$ Hz, 1H); 7.81 (dd, $J_1=1.1$ Hz, $J_2=0.6$ Hz, 1H); 8.07 (bs, 1H); 8.58 (s, 1H); 8.64 (dd, $J_1=2.7$ Hz, $J_2=0.6$ Hz, 1H).

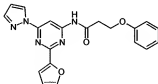
EXAMPLE 16. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-methyl-3-phenylpropionamide



Obtained from the title compound of Example 1 (0.15 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (1%) as eluent gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-methyl-3-phenylpropionamide (0.14 g, 51%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.29 (d, $J=6.4$ Hz, 3H); 2.79-2.62 (m, 2H); 3.16-3.08 (m, 1H); 6.51-6.49 (m, 1H); 6.59-6.57 (m, 1H); 7.34-7.16 (m, 6H); 7.62 (m, 1H); 7.80 (m, 1H); 7.97 (bs, 1H); 8.63-8.61 (m, 2H)

EXAMPLE 17. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenoxypropionamide

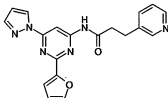


Obtained from the title compound of Example 1 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and ethyl acetate/n-

hexane (30:70) as eluent gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenoxypropionamide (0.23 g, 70%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.91 (t, 2H); 4.37 (t, 2H); 6.50-6.49 (m, 1H); 6.61-6.58 (m, 1H); 7.01-6.94 (m, 3H); 7.35-7.27 (m, 3H); 7.64 (m, 1H); 7.80 (m, 1H); 8.58 (s, 1H); 8.64 (d, $J=2.4$ Hz, 1H).

EXAMPLE 18. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)propionamide



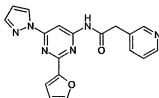
10

Obtained from the title compound of Example 1 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)propionamide (0.19 g, 60%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.76 (t, $J=7.3$ Hz, 2H); 3.09 (t, $J=7.3$ Hz, 2H); 6.51-6.50 (m, 1H); 6.60-6.58 (m, 1H); 7.28-7.21 (m, 1H); 7.34 (d, $J=3.6$ Hz, 1H); 7.63-7.57 (m, 2H); 7.81 (s, 1H); 8.13 (s, 1H); 8.54-8.47 (m, 2H); 8.56 (s, 1H); 8.64 (d, $J=2.4$ Hz, 1H).

20

EXAMPLE 19. *N*-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)acetamide



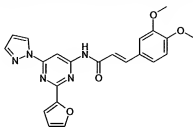
25

Obtained from the title compound of Example 1 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave *N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)acetamide (0.70 g, 23%) as an off-white solid.

δ (250 MHz, DMSO): 3.89 (s, 2H); 6.65 (dd, $J_1=2.6$ Hz, $J_2=1.3$ Hz, 1H); 6.75 (dd, $J_1=3.5$ Hz, $J_2=1.7$ Hz, 1H); 7.37 (dd, $J_1=7.9$ Hz, $J_2=4.8$ Hz, 1H); 7.49 (dd, $J_1=3.5$ Hz, $J_2=0.9$ Hz, 1H); 7.77 (dt, $J_1=7.9$ Hz, $J_2=1.7$ Hz, 1H); 7.91 (m, 1H); 7.97 (m, 1H); 8.40 (s, 1H); 8.48 (dd, $J_1=4.8$ Hz, $J_2=1.7$ Hz, 1H); 8.55 (d, $J_1=1.7$ Hz, 1H); 8.77 (d, $J_1=2.6$ Hz, 1H); 11.50 (s, 1H).

35

EXAMPLE 20. *E*-3-(3,4-Dimethoxyphenyl)-*N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acrylamide

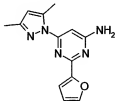


5

A solution of 3,4-dimethoxyphenylacrylic acid (0.55 g; 2.64 mmol) in thionyl chloride (4 mL) was stirred at 55°C for 1 hour. The solvent was removed under reduced pressure. The resulting oil was dissolved in methylene chloride (2 mL) and the solution was cooled to 0°C and added at the same temperature to a solution of the title compound of Example 1 (0.20 mg; 0.88 mmol) and pyridine (0.20 mg; 2.64 mmol) in methylene chloride (6 mL). The mixture was stirred at room temperature for 44 hours and diluted with methylene chloride (8 mL). The organic phase was washed with water (2x8 mL) and brine (8 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. Purification by column chromatography with silica gel, eluting with methylene chloride/ethanol (0.5%), gave *E*-3-(3,4-dimethoxyphenyl)-*N*-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acrylamide (0.70 g, 19%) as an off-white solid.

20 δ (250 MHz, CDCl₃): 3.93 (s, 3H); 3.94 (s, 3H); 6.40 (d, *J*=15.5 Hz, 1H); 6.52-6.50 (m, 1H); 6.61-6.59 (m, 1H); 6.90 (d, *J*=8.2 Hz, 1H); 7.06 (d, *J*=1.8 Hz, 1H); 7.16 (dd, *J*₁=8.2 Hz, *J*₂=1.8 Hz, 1H); 7.36 (dd, *J*₁=3.3 Hz, *J*₂=0.6 Hz, 1H); 7.64-7.63 (m, 1H); 7.76 (d, *J*=15.5 Hz, 1H); 7.82 (m, 1H); 8.33 (bs, 1H); 8.66-8.65 (m, 1H); 8.69 (s, 1H).

25 EXAMPLE 21. 2-(Furan-2-yl)-6-(3,5-dimethylpyrazol-1-yl)pyrimidin-4-ylamine



30

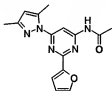
To a solution of Intermediate 4 (2.0 g; 10.2 mmol) in anhydrous DMSO (50 mL) was added 3,5-dimethylpyrazol (1.97 g; 20.5 mmol) and cesium carbonate (6.70 g; 20.6 mmol). The mixture was heated at 150°C for 9 hours. The solution was poured into water (150 mL) and extracted with ethyl acetate (3x100 mL). The organic phase was washed with water (3x100 mL), brine (100 mL), dried (Na₂SO₄), and the solvent removed under

35

reduced pressure. The resulting solid was purified by column chromatography with silica gel, eluting with ethyl acetate/n-hexane (from 3:7 to 1:1), to give 2-(furan-2-yl)-6-(3,5-dimethylpyrazol-1-yl)pyrimidin-4-ylamine (1.86 g, 71%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.29 (s, 3H); 2.78 (s, 3H); 5.10 (bs, 2H); 6.00 (s, 1H); 6.55-6.52 (m, 1H); 6.84 (s, 1H); 7.19 (d, $J=2.4$ Hz, 1H); 7.58 (s, 1H).

EXAMPLE 22. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]acetamide



10

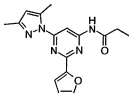
Obtained from the title compound of Example 21 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]acetamide (0.25 g, 72%) as an off-white solid.

15

δ (250 MHz, CDCl_3): 2.23 (s, 3H); 2.29 (s, 3H); 2.77 (s, 3H); 6.02 (s, 1H); 6.58-6.55 (m, 1H); 7.24 (d, $J=3.3$ Hz, 1H); 7.61-7.60 (m, 1H); 8.17 (bs, 1H); 8.48 (s, 1H).

EXAMPLE 23. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]

20 **propionamide**



Obtained from the title compound of Example 21 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:4) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide (0.26 g, 71%) as an off-white solid.

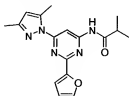
25

δ (250 MHz, CDCl_3): 1.27 (t, $J=7.6$ Hz, 3H); 2.29 (s, 3H); 2.46 (q, $J=7.6$ Hz, 2H); 2.78 (s, 3H); 6.03 (s, 1H); 6.59-6.57 (m, 1H); 7.25 (d, $J=2.7$ Hz, 1H); 7.62-7.61 (m, 1H); 8.12 (bs, 1H); 8.55 (s, 1H).

30

EXAMPLE 24. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]

isobutyramide

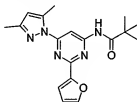


35

Obtained from the title compound of Example 21 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (1%) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]isobutyramide (0.11 g, 60%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.28 (d, $J=7.0$ Hz, 6H); 2.27 (s, 3H); 2.56 (h, $J=7.0$ Hz, 1H); 2.77 (s, 3H); 6.02 (s, 1H); 6.58-6.56 (m, 1H); 7.26 (s, 1H); 7.62-7.61 (m, 1H); 8.03 (bs, 1H); 8.58 (s, 1H).

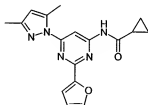
EXAMPLE 25. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl] *tert*butyramide



Obtained from the title compound of Example 21 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (15:85) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl] *tert*butyramide (95 mg, 48%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.34 (s, 9H); 2.27 (s, 3H); 2.77 (s, 3H); 6.02 (s, 1H); 6.57 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 7.25 (d, $J=0.9$ Hz, 1H); 7.62 (dd, $J_1=1.8$ Hz, $J_2=0.9$ Hz, 1H); 8.14 (bs, 1H); 8.62 (s, 1H).

EXAMPLE 26. Cyclopropanecarboxylic acid [6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]amide

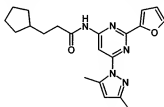


Obtained from the title compound of Example 21 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (1%) as eluent gave cyclopropanecarboxylic acid [6-(3,5-

dimethylpyrazol-1-yl]-2-(furan-2-yl)pyrimidin-4-yl]amide (70 mg, 37%) as an off-white solid.

δ (250 MHz, CDCl_3): 0.97-0.89 (m, 2H); 1.21-1.13 (m, 2H); 1.59-1.49 (m, 1H); 2.26 (s, 3H); 2.77 (s, 3H); 6.01 (s, 1H); 6.57 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 7.24 (dd, $J_1=3.3$ Hz, $J_2=0.9$ Hz, 1H); 7.61 (dd, $J_1=1.8$ Hz, $J_2=0.9$ Hz, 1H); 8.39 (bs, 1H); 8.52 (s, 1H).

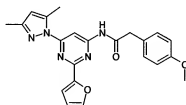
EXAMPLE 27. 3-Cyclopentyl-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide



Obtained from the title compound of Example 21 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/n-hexane (from 90% to pure methylene chloride) as eluent gave 3-cyclopentyl-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide (0.22 g, 99%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.16-1.07 (m, 2H); 1.83-1.51 (m, 9H); 2.28 (s, 3H); 2.42 (t, $J=7.3$ Hz, 2H); 2.77 (s, 3H); 6.02 (s, 1H); 6.57 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 7.24 (d, $J=3.6$ Hz, 1H); 7.61 (s, 1H); 8.16 (bs, 1H); 8.54 (s, 1H).

EXAMPLE 28. N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide

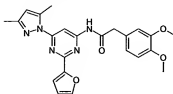


Obtained from the title compound of Example 21 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide (0.11 g, 46%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.28 (s, 3H); 2.76 (s, 3H); 3.71 (s, 2H); 3.82 (s, 3H); 6.01 (s, 1H); 6.55 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 6.89 (s, 1H); 6.93 (s, 1H); 7.26-7.20 (m, 3H); 7.59-7.58 (m, 1H); 8.04 (s, 1H); 8.54 (s, 1H).

EXAMPLE 29. 2-(3,4-Dimethoxyphenyl)-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]acetamide

5

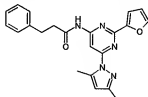


Obtained from the title compound of Example 21 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave 2-(3,4-dimethoxyphenyl)-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]acetamide (0.12 g, 47%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.28 (s, 3H); 2.77 (s, 3H); 3.71 (s, 2H); 3.89 (s, 3H); 3.90 (s, 3H); 6.02 (s, 1H); 6.55 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 6.82 (s, 1H); 6.87 (s, 1H); 6.88 (s, 1H); 7.22 (dd, $J_1=3.3$ Hz, $J_2=0.9$ Hz, 1H); 7.59 (dd, $J_1=1.8$ Hz, $J_2=0.9$ Hz, 1H); 8.02 (bs, 1H); 8.54 (s, 1H).

EXAMPLE 30. N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenylpropionamide

20

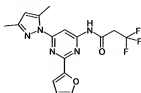


Obtained from the title compound of Example 21 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/n-hexane (from 90% to pure methylene chloride) as eluent gave N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenylpropionamide (0.23 g, 99%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.29 (s, 3H); 2.72 (t, $J=7.6$ Hz, 2H); 2.77 (s, 3H); 3.07 (t, $J=7.6$ Hz, 2H); 6.02 (s, 1H); 6.57-6.55 (m, 1H); 7.34-7.18 (m, 6H); 7.60 (m, 1H); 8.15 (bs, 1H); 8.54 (s, 1H).

EXAMPLE 31. N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide

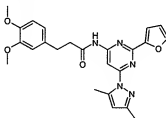
35



Obtained from the title compound of Example 21 (0.30 g) by the procedure described in
5 Example 14. Purification by column chromatography with silica gel and ethyl acetate/n-
hexane (1:4) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-
3,3,3-trifluoropropionamide (0.21 g, 49%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.29 (s, 3H); 2.78 (s, 3H); 3.30 (c, $J=10.0$ Hz, 2H); 6.04-6.02 (m,
1H); 6.59-6.57 (m, 1H); 7.28-7.24 (m, 1H); 7.62-7.61 (m, 1H); 8.30 (bs, 1H); 8.50 (s, 1H).

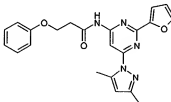
10 **EXAMPLE 32.** 3-(3,4-Dimethoxyphenyl)-*N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)
pyrimidin-4-yl]propionamide



15 Obtained from the title compound of Example 21 (0.15 g) by the procedure described in
Example 14. Purification by column chromatography with silica gel and methylene
chloride/methanol (1%) as eluent gave 3-(3,4-dimethoxyphenyl)-*N*-[6-(3,5-
dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide (0.18 g, 67%) as an off-
white solid.

δ (250 MHz, CDCl_3): 2.70 (t, $J=7.6$ Hz, 2H); 2.77 (s, 6H); 3.02 (t, $J=7.6$ Hz, 2H); 3.85 (s,
3H); 3.87 (s, 3H); 6.03 (s, 1H); 6.58-6.55 (m, 1H); 6.82-6.75 (m, 3H); 7.23 (dd, $J_1=3.3$ Hz,
25 $J_2=0.9$ Hz, 1H); 7.60 (dd, $J_1=1.8$ Hz, $J_2=0.9$ Hz, 1H); 8.09 (bs, 1H); 8.54 (s, 1H).

EXAMPLE 33. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenoxy
propionamide

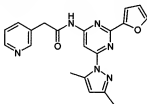


30 Obtained from the title compound of Example 21 (0.15 g) by the procedure described in
Example 14. Purification by column chromatography with silica gel and methylene

chloride/methanol (1%) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenoxypropionamide (0.21 g, 88%) as an off-white solid.

δ (250 MHz, CDCl₃): 2.28 (s, 3H); 2.78 (s, 3H); 2.89 (t, *J*=6.1 Hz, 2H); 4.36 (t, *J*=6.1 Hz, 2H); 6.02 (s, 1H); 6.58-6.56 (m, 1H); 7.00-6.93 (m, 3H); 7.33-7.24 (m, 3H); 7.62 (m, 1H);
5 8.47 (bs, 1H); 8.54 (s, 1H).

EXAMPLE 34. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)-pyrimidin-4-yl]-2-(pyridin-3-yl)acetamide

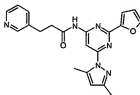


10

Obtained from the title compound of Example 21 (0.15 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene
15 chloride/methanol (2.5%) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)-pyrimidin-4-yl]-2-(pyridin-3-yl)acetamide (55 mg, 25%) as an off-white solid.

δ (250 MHz, DMSO): 2.19 (s, 3H); 2.74 (s, 3H); 3.87 (s, 2H); 6.20 (s, 1H); 6.73 (dd, *J*₁=3.4 Hz, *J*₂=1.7 Hz, 1H); 7.30 (d, *J*=3.4 Hz, 1H); 7.37 (dd, *J*₁=7.7 Hz, *J*₂=4.7 Hz, 1H); 7.79-7.74 (m, 1H); 7.96 (s, 1H); 8.35 (s, 1H); 8.50-8.46 (m, 1H); 11.41 (s, 1H)
20

EXAMPLE 35. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)-pyrimidin-4-yl]-2-(pyridin-3-yl)propionamide



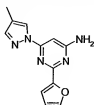
25

Obtained from the title compound of Example 21 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene
30 chloride/methanol (2%) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)-pyrimidin-4-yl]-2-(pyridin-3-yl)propionamide (97 mg, 31%) as an off-white solid.

δ (250 MHz, DMSO): 2.23 (s, 3H); 2.74 (s, 3H); 2.97-2.81 (m, 4H); 6.22 (s, 1H); 6.73-6.71 (m, 1H); 7.34-7.27 (m, 2H); 7.71-7.66 (m, 1H); 7.95 (m, 1H); 8.37 (s, 1H); 8.42-8.39 (m, 1H); 8.49 (m, 1H); 11.13 (s, 1H).

EXAMPLE 36. 2-(Furan-2-yl)-6-(4-methylpyrazol-1-yl)pyrimidin-4-ylamine

5

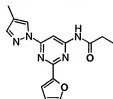


Obtained from Intermediate 4 (0.50 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent gave 2-(furan-2-yl)-6-(4-methylpyrazol-1-yl)pyrimidin-4-ylamine (0.29 g, 47%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.16 (s, 3H); 5.10 (bs, 2H); 6.57-6.55 (m, 1H); 6.83 (s, 1H); 7.29 (dd, $J_1=3.3$ Hz, $J_2=0.6$ Hz, 1H); 7.56 (s, 1H); 7.61 (m, 1H); 8.39 (s, 1H).

15 EXAMPLE 37. N-[2-(Furan-2-yl)-6-(4-methylpyrazol-1-yl)-pyrimidin-4-yl]propionamide

20

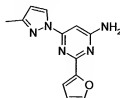


Obtained from the title compound of Example 36 (0.19 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride as eluent gave N-[2-(furan-2-yl)-6-(4-methylpyrazol-1-yl)-pyrimidin-4-yl]propionamide (0.20 g, 82%) as an off-white solid.

25 δ (250 MHz, CDCl_3): 1.25 (t, $J=7.3$ Hz, 2H); 2.16 (s, 3H); 2.45 (q, $J=7.3$ Hz, 2H); 6.59-6.57 (m, 1H); 7.33 (d, $J=3.3$ Hz, 1H); 7.62-7.60 (m, 2H); 8.12 (bs, 1H); 8.37 (s, 1H); 8.51 (s, 1H).

EXAMPLE 38. 2-(Furan-2-yl)-6-(3-methylpyrazol-1-yl)pyrimidin-4-ylamine

30

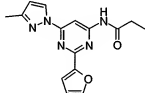


Obtained from Intermediate 4 (0.50 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent gave 2-(furan-2-yl)-6-(3-methylpyrazol-1-yl)pyrimidin-4-ylamine (0.47 g, 76%) as an off-white solid.

- 5 δ (250 MHz, CDCl_3): 2.37 (s, 3H); 5.10 (bs, 2H); 6.26 (d, $J=2.7\text{ Hz}$, 1H); 6.55 (dd, $J_1=3.3\text{ Hz}$, $J_2=1.8\text{ Hz}$, 1H); 6.82 (s, 1H); 7.29 (dd, $J_1=3.3\text{ Hz}$, $J_2=0.9\text{ Hz}$, 1H); 7.60 (dd, $J_1=1.8\text{ Hz}$, $J_2=0.9\text{ Hz}$, 1H); 8.52-8.51 (m, 1H).

EXAMPLE 39. *N*-[2-(Furan-2-yl)-6-(3-methylpyrazol-1-yl)-pyrimidin-4-yl]

10 propionamide

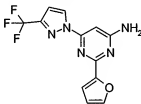


- 15 Obtained from the title compound of Example 38 (0.20 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave *N*-[2-(furan-2-yl)-6-(3-methylpyrazol-1-yl)-pyrimidin-4-yl]propionamide (0.17 g, 70%) as an off-white solid.

- 20 δ (250 MHz, CDCl_3): 1.26 (t, $J=7.6\text{ Hz}$, 3H); 2.36 (s, 3H); 2.46 (q, $J=7.6\text{ Hz}$, 2H); 6.28 (d, $J=2.4\text{ Hz}$, 1H); 6.58 (dd, $J_1=3.6\text{ Hz}$, $J_2=1.8\text{ Hz}$, 1H); 7.33-7.31 (m, 1H); 7.61 (s, 1H); 8.11 (bs, 1H); 8.51-8.49 (m, 2H).

EXAMPLE 40. 2-(Furan-2-yl)-6-(3- trifluoromethylpyrazol-1-yl)pyrimidin-4-ylamine

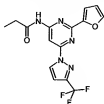
25



- Obtained from Intermediate 4 (0.50 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and methylene chloride/methanol (5%) as eluent gave 2-(furan-2-yl)-6-(3-trifluoromethylpyrazol-1-yl)pyrimidin-4-ylamine (0.49 g, 65%) as an off-white solid.

- 30 δ (250 MHz, CDCl_3): 5.22 (bs, 2H); 6.58 (dd, $J_1=3.3\text{ Hz}$, $J_2=1.8\text{ Hz}$, 1H); 6.72 (d, $J=2.7\text{ Hz}$, 1H); 6.95 (s, 1H); 7.32 (dd, $J_1=3.3\text{ Hz}$, $J_2=0.9\text{ Hz}$, 1H); 7.62 (dd, $J_1=1.8\text{ Hz}$, $J_2=0.9\text{ Hz}$, 1H); 8.70-8.69 (m, 1H).

EXAMPLE 41. *N*-[2-(Furan-2-yl)-6-(3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl]propionamide



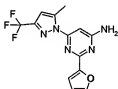
5

Obtained from the title compound of Example 40 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/n-hexane (from 90% to pure methylene chloride) as eluent gave *N*-[2-(furan-2-yl)-6-(3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl]propionamide (0.18 g, 99%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.27 (t, J 1=7.6 Hz, 3H); 2.49 (q, J 1=7.6 Hz, 2H); 6.60 (dd, J 1=3.3 Hz, J 2=1.8 Hz, 1H); 6.73 (d, J 1=2.7 Hz, 1H); 7.35 (d, J 1=3.3 Hz, 1H); 7.64 (s, 1H); 8.18 (bs, 1H); 8.62 (s, 1H); 8.96 (m, 1H).

15

EXAMPLE 42. 2-(Furan-2-yl)-6-(5-methyl-3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl amine



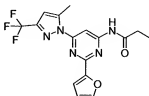
20

Obtained from Intermediate 4 (0.50 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (from 10:90 to 30:70) as eluent gave 2-(furan-2-yl)-6-(5-methyl-3-trifluoromethylpyrazol-1-yl)pyrimidin-4-ylamine (0.13 g, 16%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.84 (s, 3H); 5.26 (bs, 2H); 6.45 (s, 1H); 6.57-6.55 (m, 1H); 6.91 (s, 1H); 7.22 (dd, J 1=3.3 Hz, J 2=0.9 Hz, 1H); 7.61-7.60 (m, 1H).

30

EXAMPLE 43. *N*-[2-(Furan-2-yl)-6-(5-methyl-3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl]propionamide



35

Obtained from the title compound of Example 42 (0.25 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:4) as eluent gave *N*-[2-(furan-2-yl)-6-(5-methyl-3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl]propionamide (0.23 g, 77%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.26 (t, $J=7.6$ Hz, 3H); 2.48 (q, $J=7.6$ Hz, 2H); 2.84 (s, 3H); 6.47 (s, 1H); 6.59 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 7.28-7.26 (m, 1H); 7.63 (dd, $J_1=1.8$ Hz, $J_2=0.9$ Hz, 1H); 8.16 (bs, 1H); 8.58 (s, 1H).

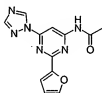
EXAMPLE 44. 2-(Furan-2-yl)-6-[[1,2,4]triazol-1-yl]pyrimidin-4-ylamine



Obtained from Intermediate 4 (1.90 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and methylene chloride/methanol (3%) as eluent gave 2-(furan-2-yl)-6-[[1,2,4]triazol-1-yl]pyrimidin-4-ylamine (1.64 g, 74%) as an off-white solid.

δ (250 MHz, CDCl_3): 6.51-6.49 (m, 1H); 6.70 (s, 1H); 7.22 (d, $J=3.0$ Hz, 1H); 8.01 (s, 1H); 8.54 (s, 1H); 9.19 (s, 1H).

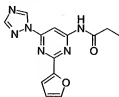
EXAMPLE 45. *N*-[2-(Furan-2-yl)-6-[[1,2,4]triazol-1-yl]pyrimidin-4-yl]acetamide



Obtained from the title compound of Example 44 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent gave *N*-[2-(furan-2-yl)-6-[[1,2,4]triazol-1-yl]pyrimidin-4-yl]acetamide (79 mg, 22%) as an off-white solid.

δ (250 MHz, DMSO): 2.20 (s, 3H); 6.78-6.76 (m, 1H); 7.54 (d, $J=3.8$ Hz, 1H); 7.98 (bs, 1H); 8.36 (s, 1H); 8.40 (s, 1H); 9.60 (s, 1H); 11.35 (s, 1H).

EXAMPLE 46. *N*-[2-(Furan-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide



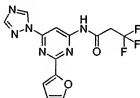
5

Obtained from the title compound of Example 44 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent gave *N*-[2-(furan-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide (90 mg, 24%) as an off-white solid.

δ (250 MHz, DMSO): 1.09 (t, $J=7.5$ Hz, 3H); 2.51 (q, $J=7.5$ Hz, 3H); 6.79-6.77 (m, 1H); 7.57-7.54 (m, 1H); 7.99-7.98 (m, 1H); 8.41-8.39 (m, 2H); 9.61 (s, 1H); 11.30 (s, 1H).

EXAMPLE 47. 3,3,3-Trifluoro-*N*-[2-(furan-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]-propionamide

15



Obtained from the title compound of Example 44 (0.30 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (2:3) as eluent gave 3,3,3-trifluoro-*N*-[2-(furan-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide (0.18 g, 40%) as an off-white solid.

δ (250 MHz, DMSO): 3.76 (q, $J=10.9$ Hz, 2H); 6.78-6.76 (m, 1H); 7.57-7.55 (m, 1H); 7.99-7.98 (m, 1H); 8.31 (s, 1H); 8.41 (s, 1H); 9.61 (s, 1H); 11.71 (s, 1H).

25

Intermediate 5. 4-Chloro-2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidine

To a solution of Intermediate 3 (0.34 g; 1.57 mmol) in anhydrous DMF (8 mL) was added pyrazol (97 mg; 1.43 mmol) and cesium carbonate (0.51 g; 1.57 mmol). The mixture was heated at 65°C for 7 hours. The solvent was removed under reduced pressure. The resulting solid was washed with water (2x25 mL) and ethyl ether to give 4-chloro-2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidine (0.21 g, 54%) as an off-white solid.

δ (300 MHz, CDCl_3): 6.58 (dd, $J_1=2.7$ Hz, $J_2=1.6$ Hz, 1H); 6.65 (dd, $J_1=3.4$ Hz, $J_2=1.8$ Hz, 1H); 7.45 (d, $J=3.4$ Hz, 1H); 7.60 (s, 1H); 7.86 (d, $J=1.6$ Hz, 1H); 7.90 (s, 1H); 8.67 (d, $J=2.7$ Hz, 1H).

35

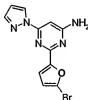
Intermediate 6. 2-(5-Bromofuran-2-yl)-4-chloro-6-(pyrazol-1-yl)pyrimidine

To a solution of Intermediate 5 (1.0 g; 4.0 mmol) in anhydrous DMF (20 mL) was added *N*-bromosuccinimide (0.78 g; 4.4 mmol). The mixture was heated at 50°C for 2 hours. The mixture was poured into water (75 mL) and extracted with ethyl acetate (2x25 mL). The organic phase was washed with water (2x25 mL), brine (25 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. Purification by column chromatography with silica gel and methylene chloride as eluent gave the title compound (0.67 g, 51%) as an off-white solid.

- 10 δ (300 MHz, CDCl₃): 6.54-6.55 (m, 2H); 7.37-7.38 (m, 1H); 7.78 (s, 1H); 7.81-7.82 (m, 1H); 8.66-8.67 (m, 1H).

EXAMPLE 48. 2-(5-Bromofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine

15



- 20 A suspension of Intermediate 6 (0.70 g; 2.13 mmol) in ethanol (22 mL) and 30% ammonium hydroxide (22 mL) was heated at 120°C in a pressure reactor for 2.30 hours. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and the resulting solution was washed with water (2x25 mL), brine (25 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure. Purification by column chromatography with silica gel and methylene chloride/ethyl acetate (1:1) as eluent gave the title compound (0.23 g, 36%) as an off-white solid.

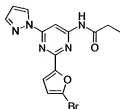
m.p.: 221.0-221.7°C.

- 25 δ (300 MHz, DMSO): 6.58 (dd, *J*₁=2.6 Hz, *J*₂=1.8 Hz, 1H); 6.78 (s, 1H); 6.81 (d, *J*=3.3 Hz, 1H); 7.34 (d, *J*=3.3 Hz, 1H); 7.37 (bs, 2H); 7.85 (d, *J*=1.8 Hz, 1H); 8.66 (d, *J*=2.6 Hz, 1H).

30

EXAMPLE 49. *N*-[2-(5-Bromofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide

35



A solution of the title compound of Example 48 (0.10 g; 0.33 mmol) in propionic anhydride (1.5 mL) was heated at 140°C for 2 hours. The mixture was poured into ice and extracted with methylene chloride (30 mL). The organic phase was washed with saturated solution of sodium bicarbonate (2x15 mL), water (15 mL), brine (15 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure. Purification by column chromatography with silica gel and methylene chloride/ethyl acetate (1:1) as eluent gave the title compound (0.10 g, 84%) as an off-white solid.

m.p.: 199.5-200.3°C.

- 10 δ (300 MHz, DMSO): 1.08 (t, $J=7.6$ Hz, 3H); 2.50 (q, $J=7.6$ Hz, 2H); 6.67 (dd, $J_1=2.6$ Hz, $J_2=1.7$ Hz, 1H); 6.90 (d, $J=3.3$ Hz, 1H); 7.53 (d, $J=3.3$ Hz, 1H); 7.94 (d, $J=1.7$ Hz, 1H); 8.48 (s, 1 H) 8.81 (d, $J=2.6$ Hz, 1H); 11.19 (bs, 1H).

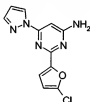
Intermediate 7. 4-Chloro-2-(5-chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidine

- 15 To a solution of Intermediate 5 (1.0 g; 4.0 mmol) in anhydrous DMF (20 mL) was added *N*-chlorosuccinimide (0.59 g; 4.4 mmol). The mixture was heated at 50°C for 2 hours. The mixture was poured into water (75 ml) and extracted with ethyl acetate (2x25 mL). The organic phase was washed with water (2x25 mL), brine (25 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. 4-Chloro-2-(5-chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidine (1.12g, 99%) was obtained as an off-white solid.

20 δ (300 MHz, CDCl₃): 6.41 (d, $J=3.6$ Hz, 1H), 6.55 (dd, $J_1=2.7$ Hz, $J_2=1.6$ Hz, 1H); 7.41 (d, $J=3.6$ Hz, 1H); 7.78 (s, 1H); 7.82 (d, $J=1.6$ Hz, 1H); 8.66 (d, $J=2.7$ Hz, 1H).

EXAMPLE 50. 2-(5-Chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine

25



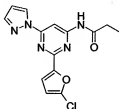
- 30 Obtained from Intermediate 7 (1.17 g) by the procedure described in Example 48. Purification by column chromatography with silica gel and methylene chloride/ethyl acetate (1:1) as eluent gave 2-(5-chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine (0.48 g, 44%) as an off-white solid.

m.p.: 209.9-211.0°C.

δ (300 MHz, DMSO): 6.58 (dd, $J_1=2.6$ Hz, $J_2=1.7$ Hz, 1H); 6.72 (d, $J=3.6$ Hz, 1H); 6.78 (s, 1H); 7.37-7.36 (m, 3H); 7.85 (s, 1H); 8.66 (d, $J=2.6$ Hz, 1H).

EXAMPLE 51. *N*-[2-(5-Chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide

5



- 10 Obtained from the title compound of Example 50 (0.28 g) by the procedure described in Example 49. Purification by column chromatography with silica gel and methylene chloride/ethyl acetate (3:1) as eluent gave *N*-[2-(5-chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (0.23 g, 72%) as an off-white solid.

m.p.: 189.3-190.1°C.

- 15 δ (300 MHz, DMSO): 1.05 (t, $J=7.6$ Hz, 3H); 2.46 (q, $J=7.6$ Hz, 2H); 6.64 (dd, $J_1=2.8$ Hz, $J_2=1.7$ Hz, 1H); 6.78 (d, $J=3.6$ Hz, 1H); 7.54 (d, $J=3.6$ Hz, 1H); 7.92 (d, $J_1=1.7$ Hz, $J_2=0.6$ Hz, 1H); 8.45 (s, 1H); 8.78 (d, $J_1=2.8$ Hz, $J_2=0.6$ Hz, 1H); 11.16 (bs, 1 H).

Intermediate 8. 5-Methylfuran-2-carboxamide (HCl)

- 20 The title compound (3.71g, 87%) was obtained as a pale yellow solid starting from 5-methyl-2-furonitrile (2.85 g) by the procedure described in Intermediate 1.

δ (300 MHz, DMSO): 2.27 (s, 3H); 6.36 (d, $J=3.6$ Hz, 1H); 7.64 (d, $J=3.6$ Hz, 1H); 8.49 (bs, 4 H).

25 Intermediate 9. 6-Amino-2-(5-methylfuran-2-yl)pyrimidin-4-ol

- To a solution of Intermediate 8 (3.71 g, 23 mmol) and cyanoacetic acid ethyl ester (2.60 g, 23 mmol) in butanol (25 mL) was added potassium *tert*butoxide (5.45 g; 46 mmol). The mixture was stirred at 135°C for 18 hours. The solvent was removed under reduced pressure. Purification by column chromatography with silica gel and methylene chloride/methanol (from 2% to 10%) as eluent gave 6-amino-2-(5-methylfuran-2-yl)pyrimidin-4-ol (1.96 g, 44%) as an off-white solid.

30 δ (300 MHz, DMSO): 2.19 (s, 3H) 4.82 (s, 1H) 6.16 (d, $J=3.3$ Hz, 1H) 6.41 (s, 2H) 7.23 (d, $J=3.3$ Hz, 1H).

35 Intermediate 10. 6-Chloro-2-(5-methylfuran-2-yl)pyrimidin-4-ylamine

- A suspension of Intermediate 9 (2.45 g, 10.2 mmol) and phosphorous pentachloride (2.12g, 10.2 mmol) in phosphorous oxychloride (7 mL) was stirred at 90°C for 2 hours. The reaction mixture was diluted with methylene chloride (50 mL) and ice was added slowly. The organic layer was decanted and washed with saturated solution of sodium bicarbonate (2x25mL), water (2x25 mL), brine (25 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure. Purification by column chromatography with silica gel and methylene chloride/ethanol (8%) as eluent gave 6-chloro-2-(5-methylfuran-2-yl)pyrimidin-4-ylamine (0.28 g, 13%) as an off-white solid.
- δ (300 MHz, DMSO): 2.35 (s, 3H); 6.27 (s, 1H); 6.28 (d, *J*=3.3 Hz, 1H); 7.05 (d, *J*=3.3 Hz, 1H); 7.32 (bs, 2 H).

EXAMPLE 52. 2-(5-Methylfuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine



- Obtained from Intermediate 9 (0.10 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and methylene chloride/ethyl acetate (9:1) as eluent gave 2-(5-methylfuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine (44 mg, 36%) as an off-white solid.
- δ (300 MHz, DMSO): 2.23 (s, 3H); 6.15-6.16 (m, 1H); 6.42-6.43 (m, 1H); 6.58 (s, 1H); 7.05 (d, *J*=3.0 Hz, 1H); 7.11 (s, 2H); 7.69 (s, 1H); 8.50 (d, *J*=2.5 Hz, 1H).

EXAMPLE 53. N-[2-(5-Methylfuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide



- Obtained from the title compound of Example 52 (40 mg) by the procedure described in Example 49. Purification by column chromatography with silica gel and methylene chloride/ethyl acetate (4:1) as eluent gave N-[2-(5-methylfuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (11 mg, 19%) as an off-white solid.

δ (300 MHz, DMSO): 0.94 (t, $J=7.6$ Hz, 3H); 2.26 (s, 3H); 2.36 (q, $J=7.6$ Hz, 2H); 6.24 (dd, $J_1=3.3$ Hz, $J_2=0.6$ Hz, 1H); 6.51 (dd, $J_1=2.8$ Hz, $J_2=1.7$ Hz, 1H); 7.25 (d, $J=3.3$ Hz, 1H); 7.80-7.78 (m, 1H); 8.28 (s, 1H); 8.63 (dd, $J=2.8$ Hz, $J_2=0.6$ Hz, 1H); 11.00 (bs, 1H).

5 **Intermediate 11. 6-Amino-2-(furan-2-yl)pyrimidin-4-ol**

To a solution of sodium methoxide (44 mmol) in methanol (10 mL) was slowly added Intermediate 1 (1.60 g, 11 mmol). The mixture was stirred at room temperature for 30 minutes and then, cyanoacetic acid ethyl ester (1.00 g, 8.8 mmol) was added. The suspension was refluxed for 18 hours. The solvent was removed under reduced pressure.

- 10 The residue was suspended in water (20 mL) and acidified to pH=6 with 5N HCl. The resulting solid was filtered and washed with water (20 mL). 6-Amino-2-(furan-2-yl)pyrimidin-4-ol was obtained (0.79 g, 50%) as a pale yellow solid.

δ (200 MHz, DMSO): 5.01 (s, 1H); 6.57 (s, 2H); 6.69 (dd, $J_1=3.4$ Hz, $J_2=1.7$ Hz, 1H); 7.43 (d, $J=3.4$ Hz, 1H); 7.91 (d, $J=1.7$ Hz, 1H).

15

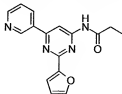
Intermediate 12. N-(6-Chloro-2-furan-2-yl-pyrimidin-4-yl)propionamide

A solution of Intermediate 11 (1.20 g, 6.78 mmol) and propionic anhydride (1.5 mL) in phosphorous oxychloride (12 mL) was stirred at 90°C for 18 hours. The solvent was removed under reduced pressure. The resulting oil was dissolved in methylene chloride (50 mL), washed with water (2x 25 mL), and brine (25 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting solid was filtered and washed with n-pentane (20 mL) to give the title compound (1.40 g, 80%) as a brown solid.

- 25 δ (200 MHz, CDCl_3): 1.26 (t, $J=7.4$ Hz, 3H); 2.49 (q, $J=7.2$ Hz, 2H); 6.59 (dd, $J_1=3.4$ Hz, $J_2=1.7$ Hz, 1H); 7.39 (d, $J=3.4$ Hz, 1H); 7.64 (s, 1H); 8.10 (d, $J=1.71$ Hz, 1H); 8.38 (bs, 1H).

EXAMPLE 54. N-[2-(Furan-2-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide

30



- 35 To a solution of Intermediate 12 (1.20 g, 4.77 mmol) in 1,2-dimethoxyethane (120 mL) were added 3-pyridinylboronic acid (0.88 g, 7.15 mmol), potassium carbonate (1.31 g, 9.54

mmol), water (8 mL) and tetrakis(triphenylphosphine) palladium (0) (2.65 g, 2.38 mmol). The mixture was stirred at 80°C overnight. The crude reaction was filtered through Celite® and the organic layer was washed with saturated solution of sodium bicarbonate (2x50 mL), water (2x50 mL), brine (50 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. Purification by column chromatography, eluting with ethyl acetate/n-hexane (from 1:6 to pure ethyl acetate), followed by digestion in hot acetonitrile gave N-[2-(furan-2-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide (0.30 g, 21%) as an off-white solid. m.p.: 251.8-253.2°C.

δ (200 MHz, DMSO): 1.10 (t, J=7.5 Hz, 3H); 2.50 (q, J=7.5 Hz, 2H) 6.75 (dd, J₁=3.0 Hz, J₂=1.7 Hz, 1H); 7.43 (d, J=3.5 Hz, 1H); 7.97 (s, 1H); 8.06 (d, J=5.6 Hz, 2H); 8.54 (s, 1H); 8.81 (d, J=5.6 Hz, 2H); 11.21 (bs, 1H).

EXAMPLE 55. 2-(Furan-2-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]amide

15



To a solution of the title compound of Example 54 (0.20 g, 0.687 mmol) in ethanol (2 mL) was added 2N HCl (2 mL). The mixture was stirred at 80°C for 1 hour. The solution was diluted with water (10 mL) and 2N NaOH was added until pH = 10. The mixture was extracted with methylene chloride (2x10mL). The combined organic extracts were washed with water (2x10mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. The resulting solid was washed with ethyl ether, to give

2-(furan-2-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamide (80 mg, 49%) as an off-white solid.

25 m.p.: 232.7-233.1°C.

δ (200 MHz, CDCl₃) 5.13 (bs, 2H); 6.58 (dd, J₁=3.5 Hz, J₂=1.7 Hz, 1H); 6.75 (s, 1H); 7.37 (d, J=3.5 Hz, 1H); 7.64-7.63 (m, 1H); 7.93 (d, J=6.0 Hz, 2H); 8.77 (d, J=6.0 Hz, 2H).

Intermediate 13. Thiophene-2-carboxamidine (HCl)

30 The title compound (12.7 g, 85%) was obtained as a solid starting from thiophene-2-carbonitrile (10.0 g) by the procedure described in Intermediate 1.

δ (250 MHz, DMSO): 7.32 (m, 1H); 8.13 (m, 1H); 8.17 (m, 1H); 8.94-8.33 (bs, 3H).

Intermediate 14. 6-Amino-2-(thiophen-2-yl)pyrimidin-4-ol

The title compound (6.13 g, 76%) was obtained as a brown solid starting from Intermediate 13 (7.00 g) by the procedure described in Intermediate 11 (reaction time: 4 days).

δ (250 MHz, DMSO): 5.04 (bs, 1H); 6.52 (bs, 2H); 7.18 (bs, 1H); 7.78 (bs, 1H); 8.09 (bs, 1H).

Intermediate 15. 6-Chloro-2-(thiophen-2-yl)pyrimidin-4-ylamine

A suspension of Intermediate 14 (6.30 g; 32.6 mmol) in phosphorous oxychloride (20 mL) was refluxed for 24 hours. The solvent was removed under pressure and ice and water were slowly added. The resulting solid was filtered, washed with 2N NaOH, and dried. 6-Chloro-2-(thiophen-2-yl)pyrimidin-4-ylamine was obtained (4.40 g, 64%) as a brown solid.

EM (M^+): 211

15 EXAMPLE 56. 6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-ylamine

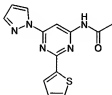


Obtained from Intermediate 15 (3.00 g) by the procedure described in Example 21. Crystallisation from ethyl ether gave 6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-ylamine (1.00 g, 27%) as an off-white solid.

δ (250 MHz, DMSO): 6.59-6.57 (m, 1H); 6.77 (s, 1H); 7.20 -7.17 (m, 1H); 7.24 (bs, 2H); 7.72-7.70 (m, 1H); 7.85- 7.84 (m, 1H); 7.97-7.95 (m, 1H); 8.67 (d, $J=2.5$ Hz, 1H).

25

EXAMPLE 57. *N*-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]acetamide



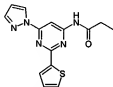
30

Obtained from the title compound of Example 56 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:4) as eluent gave *N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]acetamide (0.19 g, 55%) as an off-white solid.

35

δ (250 MHz, CDCl_3): 2.20 (s, 3H); 6.44-6.43 (m, 1H); 7.08 (dd, $J_1=4.8$ Hz, $J_2=3.6$ Hz, 1H); 7.43 (dd, $J_1=4.8$ Hz, $J_2=1.2$ Hz, 1H); 7.74-7.73 (m, 1H); 7.91 (dd, $J_1=3.6$ Hz, $J_2=1.2$ Hz, 1H); 8.39 (m, 1H); 8.59-8.57 (m, 1H).

5 **EXAMPLE 58. *N*-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide**

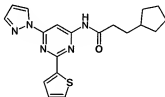


- 10 Obtained from the title compound of Example 56 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:4) as eluent gave *N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide (0.2 g, 54%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.28 (t, $J=7.6$ Hz, 3H); 2.51 (q, $J=7.6$ Hz, 2H); 6.50-6.49 (m, 1H);
15 7.15 (dd, $J_1=5.2$ Hz, $J_2=3.9$ Hz, 1H); 7.49 (dd, $J_1=5.2$ Hz, $J_2=1.2$ Hz, 1H); 7.80-7.79 (m, 1H); 8.00-7.98 (m, 2H); 8.54 (s, 1H); 8.66-8.65 (m, 1H).

EXAMPLE 59. 3-Cyclopentyl-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide

20

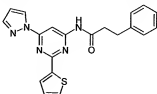


- Obtained from the title compound of Example 56 (0.20 g) by the procedure described in
25 Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:9) as eluent gave 3-cyclopentyl-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide (0.17 g, 57%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.18-1.10 (m, 2H); 1.63-1.51 (m, H); 1.85-1.75 (m, 5H); 2.48 (t, $J=7.3$ Hz, 2H); 6.50-6.49 (m, 1H); 7.15 (dd, $J_1=4.9$ Hz, $J_2=3.6$ Hz, 1H); 7.50 (dd, $J_1=4.9$ Hz, $J_2=1.2$ Hz, 1H); 7.99 (dd, $J_1=3.9$ Hz, $J_2=1.2$ Hz, 2H); 8.00 (d, $J=1.2$ Hz, 1H); 8.54 (s, 1H); 8.65 (d, $J=2.7$ Hz, 1H).

EXAMPLE 60. 3-Phenyl-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide

35

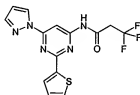


Obtained from the title compound of Example 56 (0.20 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:4) as eluent gave 3-phenyl-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide (0.29 g, 94%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.78 (t, $J=7.6$ Hz, 2H); 3.09 (t, $J=7.6$ Hz, 2H); 6.50 (dd, $J_1=2.7$ Hz, $J_2=1.8$ Hz, 1H); 7.15 (dd, $J_1=5.2$ Hz, $J_2=3.6$ Hz, 1H); 7.35-7.22 (m, 5H); 7.49 (dd, $J_1=5.2$ Hz, $J_2=1.2$ Hz, 1H); 7.81 (m, 1H); 7.94 (bs, 1H); 7.97 (dd, $J_1=3.6$ Hz, $J_2=1.2$ Hz, 1H); 8.54 (s, 1H); 8.65 (d, $J=2.6$ Hz, 1H).

EXAMPLE 61. 3,3,3-Trifluoro-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide

15

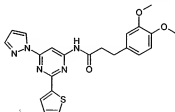


Obtained from the title compound of Example 56 (0.30 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:4) as eluent gave 3,3,3-trifluoro-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide (0.33 g, 76%) as an off-white solid.

δ (250 MHz, CDCl_3): 3.37 (q, $J=10.3$ Hz, 2H); 6.52-6.50 (m, 1H); 7.15 (dd, $J_1=4.8$ Hz, $J_2=3.6$ Hz, 1H); 7.51 (dd, $J_1=4.8$ Hz, $J_2=1.2$ Hz, 1H); 7.81-7.80 (m, 1H); 7.99 (dd, $J_1=3.6$ Hz, $J_2=1.2$ Hz, 1H); 8.23 (bs, 1H); 8.48 (bs, 1H); 8.65-8.64 (m, 1H).

EXAMPLE 62. 3-(3,4-Dimethoxyphenyl)-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide

30



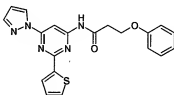
Obtained from the title compound of Example 56 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel eluting with methylene chloride/methanol (0.2%), followed by a second purification by column chromatography

using ethyl acetate/n-hexane (1:1) as eluent gave 3-(3,4-dimethoxyphenyl)-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide (0.18 g, 51%) as an off-white solid.

δ (250 MHz, CDCl₃): 2.76 (t, *J*=7.6 Hz, 2H); 3.04 (t, *J*=7.6 Hz, 2H); 3.85 (s, 3H); 3.87 (s, 3H); 6.50 (dd, *J*₁=2.7 Hz, *J*₂=1.8 Hz, 1H); 6.80-6.77 (m, 3H); 7.15 (dd, *J*₁=4.8 Hz, *J*₂=3.6 Hz, 1H); 7.49 (dd, *J*₁=4.8 Hz, *J*₂=1.2 Hz, 1H); 7.81-7.80 (m, 1H); 7.92 (bs, 1H); 7.97 (dd, *J*₁=3.6 Hz, *J*₂=1.2 Hz, 1H); 8.53 (s, 1H); 8.65 (dd, *J*₁=2.7 Hz, *J*₂=0.6 Hz, 1H).

EXAMPLE 63. 3-Phenoxy-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide

10

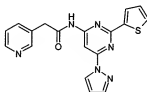


Obtained from the title compound of Example 56 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave 3-phenoxy-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide (0.28 g, 85%) as an off-white solid.

δ (250 MHz, CDCl₃): 2.95 (t, *J*=6.0 Hz, 2H); 4.38 (t, *J*=6.0 Hz, 2H); 6.50-6.49 (m, 1H); 7.03-6.98 (m, 3H); 7.16 (dd, *J*₁=4.8 Hz, *J*₂=3.6 Hz, 1H); 7.37-7.29 (m, 2H); 7.50 (dd, *J*₁=5.2 Hz, *J*₂=1.2 Hz, 1H); 7.80-7.79 (m, 1H); 8.00 (dd, *J*₁=3.9 Hz, *J*₂=1.2 Hz, 1H); 8.53 (s, 1H); 8.63 (bs, 1H); 8.66 (dd, *J*₁=2.7 Hz, *J*₂=0.6 Hz, 1H).

EXAMPLE 64. *N*-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-2-(pyridin-3-yl)acetamide

25



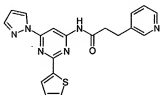
Obtained from the title compound of Example 56 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (2.5%) as eluent gave *N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-2-(pyridin-3-yl)acetamide (0.17 g, 56%) as an off-white solid.

δ (250 MHz, CDCl₃): 3.82 (s, 2H); 6.49 (dd, *J*₁=2.7 Hz, *J*₂=1.5 Hz, 1H); 7.16-7.13 (m, 1H); 7.37-7.32 (m, 1H); 7.50 (dd, *J*₁=4.9 Hz, *J*₂=1.2 Hz, 1H); 7.77-7.73 (m, 1H); 7.78 (dd,

$J_1=1.5$ Hz, $J_2=0.6$ Hz, 1H); 7.98 (dd, $J_1=3.6$ Hz, $J_2=1.2$ Hz, 1H); 8.04 (bs, 1H); 8.51 (s, 1H); 8.62-8.59 (m, 2H); 8.64 (dd, $J_1=2.7$ Hz, $J_2=0.6$ Hz, 1H).

EXAMPLE 65. *N*-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)propionamide

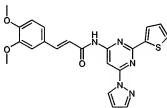
5 propionamide



10 Obtained from the title compound of Example 56 (0.20 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave *N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)propionamide (0.13 g, 43%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.81 (t, $J=7.3$ Hz, 2H); 3.10 (t, $J=7.3$ Hz, 2H); 6.51 (dd, $J_1=2.7$ Hz, $J_2=1.5$ Hz, 1H); 7.15 (dd, $J_1=5.2$ Hz, $J_2=3.6$ Hz, 1H); 7.25-7.21 (m, 1H); 7.50-7.48 (m, 1H); 7.61 (dt, $J_1=7.9$ Hz, $J_2=2.1$ Hz, 1H); 7.82-7.81 (m, 1H); 7.97 (dd, $J_1=3.6$ Hz, $J_2=1.2$ Hz, 1H); 8.15 (bs, 1H); 8.5 (dd, $J_1=4.8$ Hz, $J_2=1.5$ Hz, 1H); 8.54-8.52 (m, 2H); 8.65 (d, $J=2.7$ Hz, 1H).

20 **EXAMPLE 66. *E*-3-(3,4-Dimethoxyphenyl)-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]acrylamide**



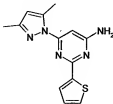
25

Obtained from the title compound of Example 56 (0.30 g) by the procedure described in Example 20. Purification by column chromatography with silica gel and methylene chloride/methanol (0.5%) as eluent gave *E*-3-(3,4-dimethoxyphenyl)-*N*-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]acrylamide (0.20 g, 36%) as an off-white solid.

δ (250 MHz, CDCl_3): 3.82 (s, 3H); 3.84 (s, 3H); 6.68 (dd, $J_1=2.7$ Hz, $J_2=1.7$ Hz, 1H); 7.09-7.02 (m, 2H); 7.28-7.23 (m, 3H); 7.66 (d, $J_1=15.5$ Hz, 1H); 7.84 (dd, $J_1=5.0$ Hz, $J_2=1.3$ Hz, 1H); 7.97 (d, $J_1=1.3$ Hz, 1H); 8.12 (dd, $J_1=3.7$ Hz, $J_2=1.0$ Hz, 1H); 8.57 (s, 1H); 8.82 (d, $J_1=2.7$ Hz, 1H); 11.08 (s, 1H).

35

EXAMPLE 67. 6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-ylamine



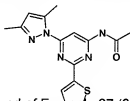
5

Obtained from Intermediate 15 (3.0 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (3:10) as eluent gave 6-(3,5-dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-ylamine (1.75 g, 45%) as an off-white solid.

δ (250 MHz, DMSO): 2.19 (s, 3H); 2.72 (s, 3H); 6.13 (s, 1H); 6.73 (s, 1H); 7.08 (bs, 2H); 7.19-7.15 (m, 1H); 7.70-7.67 (m, 1H); 7.82-7.79 (m, 1H).

EXAMPLE 68. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]acetamide

15



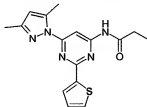
Obtained from the title compound of Example 67 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (3:10) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]acetamide (80 mg, 23%) as an off-white solid.

δ (250 MHz, CDCl₃): 2.20 (s, 3H); 2.23 (s, 3H); 2.74 (s, 3H); 5.96 (s, 1H); 7.07 (dd, $J_1=4.8$ Hz, $J_2=3.6$ Hz, 1H); 7.40 (dd, $J_1=5.2$ Hz, $J_2=1.2$ Hz, 1H); 7.84 (dd, $J_1=3.6$ Hz, $J_2=1.2$ Hz, 1H); 7.94 (bs, 1H); 8.39 (s, 1H).

25

EXAMPLE 69. *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide

30

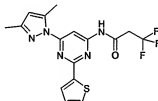


Obtained from the title compound of Example 67 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-

hexane (1:4) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide (0.17 g, 47%) as an off-white solid.

δ (250 MHz, DMSO): 1.27 (t, $J=7.3$ Hz, 3H); 2.28 (s, 3H); 2.49 (q, $J=7.3$ Hz, 2H); 2.80 (s, 3H); 6.02 (s, 1H); 7.13 (dd, $J_1=4.9$ Hz, $J_2=3.6$ Hz, 1H); 7.46 (dd, $J_1=4.9$ Hz, $J_2=1.2$ Hz, 1H); 7.92-7.89 (m, 2H); 8.50 (s, 1H).

EXAMPLE 70. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide

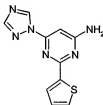


10

Obtained from the title compound of Example 67 (0.30 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (15:85) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide (55 mg, 13%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.32 (s, 3H); 2.84 (s, 3H); 3.38 (q, $J=10.0$ Hz, 2H); 6.06 (s, 1H); 7.18-7.16 (m, 1H); 7.52-7.50 (m, 1H); 7.96-7.94 (m, 1H); 8.12 (s, 1H); 8.48 (bs, 1H).

20 EXAMPLE 71. 2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine



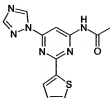
25

Obtained from Intermediate 15 (1.86 g) by the procedure described in Example 21. Crystallisation from ethyl ether gave 2-(thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine (1.81 g, 84%) as an off-white solid.

δ (250 MHz, MeOD): 6.67 (s, 1H); 7.06 (dd, $J_1=5.0$ Hz, $J_2=3.6$ Hz, 1H); 7.40 (dd, $J_1=5.0$ Hz, $J_2=1.3$ Hz, 1H); 7.88-7.86 (m, 1H); 8.01 (s, 1H); 9.19 (s, 1H).

30

EXAMPLE 72. *N*-[2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]acetamide

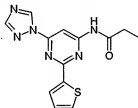


35

Obtained from the title compound of Example 71 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (from 1:1 to 4:1) as eluent gave *N*-[2-(thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]acetamide (0.21 g, 63%) as an off-white solid.

δ (250 MHz, DMSO): 2.15 (s, 3H); 7.20 (dd, $J_1=4.9$ Hz, $J_2=3.8$ Hz, 1H); 7.79 (dd, $J_1=4.9$ Hz, $J_2=1.4$ Hz, 1H); 8.11 (dd, $J_1=3.8$ Hz, $J_2=1.4$ Hz, 1H); 8.29 (s, 1H); 8.34 (s, 1H); 9.57 (s, 1H); 11.00 (s, 1H).

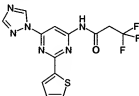
EXAMPLE 73. *N*-[2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide



Obtained from the title compound of Example 71 (0.14 g) by the procedure described in Example 2. Crystallisation from ethyl ether gave *N*-[2-(thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide (0.13 g, 75%) as an off-white solid.

δ (250 MHz, DMSO): 1.05 (t, $J=7.4$ Hz, 3H); 2.49 (q, $J=7.4$ Hz, 2H); 7.25-7.20 (m, 1H); 7.83-7.80 (m, 1H); 8.14-8.12 (m, 1H); 8.34 (s, 1H); 8.36 (s, 1H); 9.58 (s, 1H); 11.09 (s, 1H).

EXAMPLE 74. 3,3,3-Trifluoro-*N*-[2-(thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide



Obtained from the title compound of Example 71 (0.30 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (10%) as eluent gave 3,3,3-trifluoro-*N*-[2-(thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide (0.2 mg, 47%) as an off-white solid.

δ (250 MHz, DMSO): 3.57 (q, $J=11.0$ Hz, 2H); 7.09-7.04 (m, 1H); 7.68-7.65 (m, 1H); 8.00-7.97 (m, 1H); 8.10 (s, 1H); 8.21 (s, 1H); 9.45 (s, 1H); 11.31 (s, 1H).

Intermediate 16. 3-Methylthiophene-2-carboxamide (HCl)

The title compound (3.25 g, 43%) was obtained as an off-white solid starting from 3-methylthiophene-2-carbonitrile (5.26 g) by the procedure described in Intermediate 1.

5 δ (300 MHz, DMSO): 2.36 (s, 3H); 7.42 (bs, 4H); 8.24 (s, 1H).

Intermediate 17. 6-Amino-2-(3-methylthiophen-2-yl)pyrimidin-4-ol

Obtained from Intermediate 16 (3.20 g) by the procedure described in Intermediate 11. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent, followed by a semi-preparative HPLC purification gave 6-amino-2-(3-methylthiophen-2-yl)pyrimidin-4-ol (80 mg, 2%) as an off-white solid.

δ (300 MHz, DMSO): 2.36 (s, 3H); 5.07 (s, 1H); 6.36 (bs, 2H); 6.82 (d, $J=4.9$ Hz, 1H); 7.40 (d, $J=4.9$ Hz, 1H).

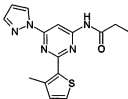
15 **Intermediate 18. *N*-[6-Chloro-2-(3-methylthiophen-2-yl)pyrimidin-4-yl]propionamide**

Obtained from Intermediate 17 (80 mg) by the procedure described in Intermediate 12. Purification by column chromatography with silica gel and methylene chloride as eluent gave *N*-[6-Chloro-2-(3-methylthiophen-2-yl)pyrimidin-4-yl]propionamide (40 mg, 37%) as an off-white solid.

20 δ (300 MHz, DMSO): 0.93 (t, $J=7.4$ Hz, 3H); 2.36-2.37 (m, 5H); 6.92 (d, $J=5.0$ Hz, 1H); 7.54 (d, $J=5.0$ Hz, 1H); 7.78 (s, 1H).

EXAMPLE 75. *N*-[2-(3-Methylthiophen-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide

25



Obtained from Intermediate 18 (40 mg) by the procedure described in Example 21.

30 Purification by column chromatography with silica gel and ethyl acetate/methylene chloride (1:5) as eluent gave *N*-[2-(3-methylthiophen-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (5 mg, 11%) as an off-white solid.

δ (300 MHz, DMSO): 1.10 (t, $J=7.6$ Hz, 3H); 2.54 (q, $J=7.6$ Hz, 2H); 2.74 (s, 3H); 6.68-6.67 (m, 1H); 7.08 (d, $J=5.1$ Hz, 1H); 7.95-7.94 (m, 1H); 8.42 (s, 1H); 8.63 (d, $J=5.1$ Hz, 1H); 10.89 (bs, 1H).

Intermediate 19. 3-Amino-3-(furan-2-yl)acrylonitrile

- To a cooled solution (-78°C) of diisopropylamine (0.92 g, 9.13 mmol) in anhydrous THF (17 mL) was slowly added 1.56M n-butyllithium in hexane (5.85 mL). The mixture was stirred at -78°C for 30 minutes and then, a solution of acetonitrile (0.33 g, 8.06 mmol) in anhydrous THF (3.5 mL) was slowly added. After 30 minutes at the same temperature, a solution of furan-2-carbonitrile (0.50 g, 5.37 mmol) was added. The mixture was allowed to stand at -78°C for 20 minutes and at room temperature overnight. Water (6 mL) was added and the solvent removed under reduced pressure. The resulting solid was suspended in water (50 mL) and extracted with methylene chloride (3x25 mL). The organic layer was washed with brine (2x20 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. The title compound was obtained (0.70g, 97%) as a brown solid, which was used in the next step without further characterisation.

15 Intermediate 20. 4-Amino-6-(furan-2-yl)pyrimidine-2-thiol

- To a solution of Intermediate 19 (1.38 g, 10.3 mmol) in ethanol (17 mL) were added sodium ethoxide (1.54 g, 22.63 mmol) and thiourea (1.56 g, 22.63 mmol). The mixture was refluxed for 45 hours. The resulting suspension was cooled and water was added (12 mL). The solution was acidified with 1N HCl until pH=5. The resulting solid was filtered, washed with water (2x20 mL), ethyl ether (10 mL) and dried. 4-Amino-6-(furan-2-yl)pyrimidine-2-thiol was obtained (1.20 g, 60%) as a solid.

δ (250 MHz, DMSO): 6.27 (s, 1H); 6.71 (dd, *J*₁=3.4 Hz, *J*₂=1.7 Hz, 1H); 7.76-7.53 (m, 2H); 7.95 (dd, *J*₁=1.7 Hz, *J*₂=0.8 Hz, 1H); 12.14 (bs, 1H).

25 Intermediate 21. 6-(Furan-2-yl)-2-methylsulfanylpuridin-4-ylamine

- To a solution of Intermediate 20 (1.87 g, 9.68 mmol) in 10% sodium hydroxide (15 mL) was added methyl iodide (1.51 g, 10.6 mmol). The mixture was stirred at room temperature for 2 hours. The solvent was partially removed under reduced pressure and 2N HCl was added until pH=10. The resulting solid was filtered, washed with water (2x20 mL) and dried. 6-(Furan-2-yl)-2-methylsulfanylpuridin-4-ylamine was obtained (1.90 g, 95%) as an off-white solid.

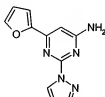
δ (400 MHz, MeOD): 3.46 (s, 3H); 7.48 (s, 1H); 7.52 (dd, *J*₁=3.4 Hz, *J*₂=1.7 Hz, 1H); 8.08 (dd, *J*₁=3.4 Hz, *J*₂=0.8 Hz, 1H); 8.59 (dd, *J*₁=1.7 Hz, *J*₂=0.8 Hz, 1H).

35 Intermediate 22. 6-(Furan-2-yl)-2-methanesulfonylpuridin-4-ylamine

To a cooled suspension (0°C) of Intermediate 21 (1.90 g, 9.20 mmol) in chloroform (70 mL) was added 70% m-chloroperbenzoic acid (4.53 g, 18.39 mmol). The mixture was stirred at 0°C for 45 minutes. The solvent was partially removed under reduced pressure and the resulting solid was filtered, washed with ethyl ether, and dried. 1.36 g of the title compound were obtained. The organic solution was washed with 2N sodium hydroxide (2x25 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. 0.47 g of the title compound were obtained (overall yield: 83%).

δ (400 MHz, MeOD): 4.27 (s, 3H); 7.6 (dd, *J*₁=3,4 Hz, *J*₂=1,7 Hz, 1H); 7.86 (s, 1H); 8.27 (dd, *J*₁=3,4 Hz, *J*₂=0,8 Hz, 1H); 8.68 (dd, *J*₁=1,7 Hz, *J*₂=0,8 Hz, 1H).

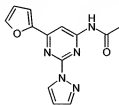
EXAMPLE 76. 6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-ylamine



To a solution of Intermediate 22 (1.16 g, 4.85 mmol) in anhydrous DMSO (20 mL) was added pyrazol (0.36 g, 5.33 mmol) and cesium carbonate (1.71 g; 5.33 mmol). The mixture was heated at 110°C for 2.5 hours and at room temperature overnight. The solution was poured into water (60 mL) and extracted with ethyl acetate (3x40 mL). The organic phase was washed with water (2x50 mL), brine (50 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography with silica gel and methylene chloride/methanol (5%) as eluent and the resulting solid was washed with ethyl ether. 6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-ylamine (0.56 g, 51%) was obtained as an off-white solid.

δ (250 MHz, CDCl₃): 5.33 (bs, 2H); 6.47- 6.46 (m, 1H); 6.58-6.56 (m, 1H); 6.68 (s, 1H); 7.27 (s, 1H); 7.56 (s, 1H); 7.79 (s, 1H); 8.63 (d, *J*=2.4 Hz, 1H).

EXAMPLE 77. N-[6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]acetamide



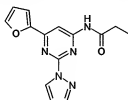
Obtained from the title compound of Example 76 (0.20 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene

chloride/methanol (2%) as eluent gave *N*-[6-(furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]acetamide (0.19 g, 80%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.21 (s, 3H); 6.46 (bs, 1H); 6.56-6.55 (m, 1H); 7.31 (d, $J=3.6$ Hz, 1H); 7.60 (s, 1H); 7.77 (s, 1H); 8.29 (s, 1H); 8.55 (bs, 1H); 8.60 (d, $J=2.4$ Hz, 1H).

5

EXAMPLE 78. *N*-[6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]propionamide



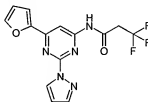
10

Obtained from the title compound of Example 76 (0.28 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave *N*-[6-(furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (84 mg, 24%) as a pale yellow solid.

15

δ (250 MHz, CDCl_3): 1.27 (t, $J=7.3$ Hz, 3H); 2.47 (q, $J=7.3$ Hz, 2H); 6.49-6.48 (m, 1H); 6.58-6.57 (m, 1H); 7.33 (d, $J=3.6$ Hz, 1H); 7.61 (s, 1H); 7.79 (s, 1H); 8.34 (bs, 1H); 8.36 (d, $J=1.2$ Hz, 1H); 8.64 (d, $J=2.4$ Hz, 1H).

20 EXAMPLE 79. 3,3,3-Trifluoro-*N*-[6-(furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]propionamide



25

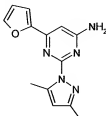
Obtained from the title compound of Example 76 (0.25 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (4%) as eluent gave 3,3,3-trifluoro-*N*-[2-(furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]propionamide (0.19 mg, 49%) as an off-white solid.

30

δ (250 MHz, CDCl_3): 3.32 (q, $J=9.8$ Hz, 2H); 6.51-6.49 (m, 1H); 6.61-6.59 (m, 1H); 7.37 (d, $J=3.6$ Hz, 1H); 7.63 (s, 1H); 7.80 (s, 1H); 8.32 (s, 1H); 8.63 (d, $J=2.4$ Hz, 1H); 8.68 (bs, 1H).

EXAMPLE 80. 2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-ylamine

35

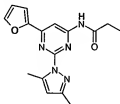


5 Obtained from Intermediate 22 (3.00 g) by the procedure described in Example 76. Purification by column chromatography with silica gel and chloroform/isopropanol (1:1) as eluent, followed by a second column chromatography with silica gel and methylene chloride/methanol (5%) as eluent gave 2-(3,5-dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-ylamine (0.15 g, 5%) as an off-white solid.

10 δ (250 MHz, CDCl_3): 2.33 (s, 3H); 2.72 (s, 3H); 5.18 (bs, 2H); 6.01 (s, 1H); 6.54 (dd, $J_1=6.3$ Hz, $J_2=1.8$ Hz, 1H); 6.63 (s, 1H); 7.15-7.13 (m, 1H); 7.55-7.54 (m, 1H).

EXAMPLE 81. *N*-[2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-yl] propionamide

15

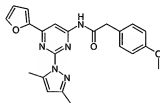


Obtained from the title compound of Example 80 (95 mg) by the procedure described in
20 Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (10%) as eluent gave *N*-[2-(3,5-dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-yl] propionamide (50 mg, 43%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.25 (t, $J=7.6$ Hz, 3H); 2.35 (s, 3H); 2.45 (q, $J=7.6$ Hz, 2H); 2.75 (s, 3H); 6.05 (s, 1H); 6.58-6.56 (m, 1H); 7.24-7.23 (m, 1H); 7.61 (s, 1H); 8.27 (bs, 1H);
25 8.33 (s, 1H).

EXAMPLE 82. *N*-[2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide

30



Obtained from the title compound of Example 80 (100 mg) by the procedure described
in Example 2. Purification by column chromatography with silica gel and methylene

chloride/methanol (10%) as eluent gave *N*-[2-(3,5-dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide (50 mg, 30%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.32 (s, 3H); 2.71 (s, 3H); 3.69 (s, 2H); 3.81 (s, 3H); 6.03 (s, 1H); 6.57-6.55 (m, 1H); 6.90 (d, $J=8.8$ Hz, 2H); 7.24-7.20 (m, 3H); 7.60 (d, $J=1.5$ Hz, 1H); 8.35 (s, 2H).

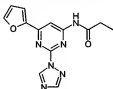
EXAMPLE 83. 6-(Furan-2-yl)-2-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine



To a solution of Intermediate 22 (0.21 g, 0.88 mmol) in anhydrous DMF (3 mL) was added [1,2,4]triazol (60 mg, 0.88 mmol) and potassium carbonate (0.12 g; 0.88 mmol). The mixture was heated at 80°C for 2 hours. The solution was poured into water (10 mL) and extracted with ethyl acetate (2x10 mL). The organic phase was washed with water (2x10 mL), brine (10 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. Purification by column chromatography with silica gel and methylene chloride as eluent gave 6-(furan-2-yl)-2-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine (70 mg, 35%) as an off-white solid.

δ (200 MHz, DMSO): 6.70 (s, 1H); 6.73-6.72 (m, 1H); 7.30 (d, $J=3.4$ Hz, 1H); 7.57 (bs, 2H); 7.93-7.92 (m, 1H); 8.22 (s, 1H); 9.35 (s, 1H).

EXAMPLE 84. *N*-[6-(Furan-2-yl)-2-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide



Obtained from the title compound of Example 83 (45 mg) by the procedure described in Example 49. Purification by column chromatography with silica gel and methylene chloride/methanol (1%) as eluent gave *N*-[6-(furan-2-yl)-2-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide (16 mg, 28%) as an off-white solid.

δ (300 MHz, DMSO): 1.16 (t, $J=7.4$ Hz, 3H); 2.53 (q, $J=7.4$ Hz, 2H); 6.66 (dd, $J_1=3.4$ Hz, $J_2=1.8$ Hz, 1H); 7.43 (dd, $J_1=3.4$, $J_2=0.8$ Hz, 1H); 7.79 (dd, $J_1=1.8$ Hz, $J_2=0.8$ Hz, 1H); 8.12 (s, 1H); 8.44 (s, 1H); 9.34 (s, 1H); 11.16 (bs, 1H).

Intermediate 23. 3-Amino-3-(pyridin-2-yl)acrylonitrile

To a solution of pyridin-2-carbonitrile (5.0 g, 48.0 mmol) in toluene (175 mL) was added potassium *tert*butoxide (16.2 g, 0.144 mol) and acetonitrile (3.94 g, 96.0 mmol). The mixture was stirred at room temperature for 3 hours. To the reaction mixture was added saturated solution of potassium bicarbonate (200 mL) and the mixture was extracted with ethyl ether (2x200 mL). The organic layer was dried (Na₂SO₄) and the solvent removed under reduced pressure. The title compound was obtained (5.44 g, 78%) as a light brown solid, which was used in the next step without further characterisation.

10 Intermediate 24. 4-Amino-6-(pyridin-2-yl)pyrimidine-2-thiol

Obtained from Intermediate 23 (1.14 g) by the procedure described in Intermediate 20. Crystallisation from ethyl ether gave 4-amino-6-(pyridin-2-yl)pyrimidine-2-thiol (1.28 g, 80%) as an off-white solid.

δ (250 MHz, DMSO): 6.70 (bs, 1H); 7.60 (m, 1H); 7.79 (bs, 1H); 8.15-7.98 (m, 2H);
15 8.74 (m, 1H); 11.21 (bs, 1H).

Intermediate 25. 2-Methylsulfanyl-6-(pyridin-2-yl)pyrimidin-4-ylamine

Obtained from Intermediate 24 (4.0 g) by the procedure described in Intermediate 21. Crystallisation from ethyl ether gave the title compound (4.16 g, 97%) as an orange solid.

20 EM (M⁺): 218.

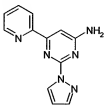
Intermediate 26. 2-Methanesulfonyl-6-(pyridin-2-yl)pyrimidin-4-ylamine

Obtained from Intermediate 25 (4.16 g) by the procedure described in Intermediate 22. Crystallisation from ethyl ether gave 2-methanesulfonyl-6-(pyridin-2-yl)pyrimidin-4-ylamine
25 (3.89 g, 82%) as an off-white solid.

δ (250 MHz, DMSO): 3.38 (s, 3H); 7.59-7.53 (m, 2H); 7.86 (bs, 1H); 8.05-7.97 (m, 1H);
8.34 (m, 1H); 8.73 (m, 1H).

EXAMPLE 85. 2-(Pyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-ylamine

30

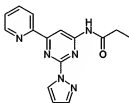


Obtained from Intermediate 26 (0.43 g) by the procedure described in Example 76. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave 2-(pyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-ylamine (0.25 g, 47%) as an off-white solid.

- 5 δ (250 MHz, DMSO): 6.54 (t, $J=1.7$ Hz, 1H); 7.38 (s, 1H); 7.46 (bs, 2H); 7.56-7.50 (m, 1H); 7.78-7.77 (m, 1H); 7.99 (dt, $J_1=7.7$ Hz, $J_2=1.7$ Hz, 1H); 8.45 (d, $J=7.7$ Hz, 1H); 8.71 (d, $J=2.7$ Hz, 2H).

EXAMPLE 86. *N*-[2-(Pyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]propionamide

10



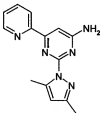
15

Obtained from the title compound of Example 85 (0.19 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave *N*-[2-(pyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]propionamide (0.15 g, 65%) as an off-white solid.

- 20 δ (250 MHz, CDCl_3): 1.28 (t, $J=7.6$ Hz, 2H); 2.49 (q, $J=7.6$ Hz, 2H); 6.53-6.51 (m, 1H); 7.45-7.39 (m, 1H); 7.90-7.83 (m, 2H); 8.30 (bs, 1H); 8.47 (dd, $J_1=7.9$ Hz, $J_2=0.9$ Hz, 1H); 8.77-8.72 (m, 2H); 9.08 (s, 1H).

EXAMPLE 87. 2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-ylamine

25

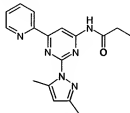


- 30 Obtained from Intermediate 26 (3.90 g) by the procedure described in Example 76. Purification by column chromatography with silica gel and methylene chloride/acetonitrile (from 4:1 to 1:4) as eluent, followed by a second column chromatography with silica gel and methylene chloride/acetonitrile/methanol (1:4:0.25) as eluent gave 2-(3,5-dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-ylamine (0.42 g, 10%) as an off-white solid.
- 35

δ (250 MHz, CDCl_3): 2.35 (s, 3H); 2.79 (s, 3H); 5.26 (bs, 2H); 6.05 (s, 1H); 7.41-7.36 (m, 2H); 7.85 (dt, $J_1=7.6$ Hz, $J_2=1.8$ Hz, 1H); 8.38-8.34 (m, 1H); 8.70-8.67 (m, 1H).

EXAMPLE 88. *N*-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]propionamide

5 propionamide

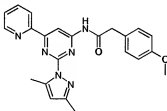


10 Obtained from the title compound of Example 87 (0.17 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 5% methanol) as eluent gave *N*-[2-(3,5-dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]propionamide (0.10 g, 64%) as an off-white solid.

15 δ (250 MHz, CDCl_3): 1.26 (t, $J=7.6$ Hz, 3H); 2.36 (s, 3H); 2.46 (q, $J=7.6$ Hz, 2H); 2.81 (s, 3H); 6.08 (s, 1H); 7.40 (ddd, $J_1=7.6$ Hz, $J_2=1.8$ Hz, 1H); 7.85 (dt, $J_1=7.6$ Hz, $J_2=1.8$ Hz, 1H); 8.36-8.31 (m, 2H); 8.76-8.73 (m, 1H); 9.05 (s, 1H).

EXAMPLE 89. *N*-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide.

20 methoxyphenyl)acetamide.



25

Obtained from the title compound of Example 87 (0.17 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (from 1% to 5%) as eluent, followed by a second column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 10% methanol) as eluent gave *N*-[2-(3,5-dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide (94 mg, 31%) as an off-white solid.

30 δ (250 MHz, CDCl_3): 2.34 (s, 3H); 2.78 (s, 3H); 3.71 (s, 2H); 3.81 (s, 3H); 6.07 (s, 1H); 6.89-6.87 (m, 1H); 6.93-6.91 (m, 1H); 7.26-7.21 (m, 2H); 7.40 (ddd, $J_1=7.6$ Hz, $J_2=4.8$ Hz, 1H); 7.84 (dt, $J_1=7.6$ Hz, $J_2=1.8$ Hz, 1H); 8.25 (bs, 1H); 8.33 (dt, $J_1=7.6$ Hz, $J_2=1.2$ Hz, 1H); 8.74 (dt, $J_1=4.8$ Hz, $J_2=1.8$ Hz, 1H); 9.06 (s, 1H).

Intermediate 27. 3-Amino-3-(pyridin-3-yl)acrylonitrile

- Obtained from pyridin-3-carbonitrile (5.00 g) by the procedure described in Intermediate 23 (reaction time: 3 days). Crystallisation from ethyl ether gave 3-amino-3-(pyridin-3-yl)acrylonitrile (2.81 g, 40%) as an off-white solid.

δ (250 MHz, DMSO): 4.58 (s, 1H); 6.96 (s, 2H); 7.46 (dd, $J_1=7.9$ Hz, $J_2=4.6$ Hz, 1H); 7.98-7.93 (m, 1H); 8.64 (dd, $J_1=4.7$ Hz, $J_2=1.6$ Hz, 1H); 8.77 (dd, $J_1=2.5$ Hz, $J_2=0.8$ Hz, 1H).

Intermediate 28. 4-Amino-6-(pyridin-3-yl)pyrimidine-2-thiol

Obtained from Intermediate 27 (2.81 g) by the procedure described in Intermediate 20. Crystallisation from ethyl ether gave 4-amino-6-(pyridin-3-yl)pyrimidine-2-thiol (3.28 g, 83%) as an off-white solid.

- δ (200 MHz, DMSO): 7.53 (dd, $J_1=8.1$ Hz, $J_2=4.7$ Hz, 2H); 7.67 (s, 2H); 8.12-8.07 (m, 1H); 8.71 (d, $J=4.7$ Hz, 1H); 8.85 (s, 1H); 12.40 (bs, 1H).

Intermediate 29. 2-Methylsulfonyl-6-(pyridin-3-yl)pyrimidin-4-ylamine

- Obtained from Intermediate 28 (3.00 g) by the procedure described in Intermediate 21. Crystallisation from ethyl ether gave the title compound (2.96 g, 92%) as a solid, which was used in the next step without further characterisation.

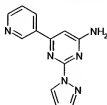
Intermediate 30. 2-Methanesulfonyl-6-(pyridin-3-yl)pyrimidin-4-ylamine

- Obtained from Intermediate 29 (2.00 g) by the procedure described in Intermediate 22. Crystallisation from ethyl ether gave 2-methanesulfonyl-6-(pyridin-3-yl)pyrimidin-4-ylamine (1.90 g, 83%) as an off-white solid.

EM (M⁺): 250

EXAMPLE 90. 2-(Pyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamine

30



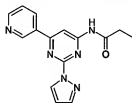
- Obtained from Intermediate 30 (1.00 g) by the procedure described in Example 76. Purification by column chromatography with silica gel and methylene chloride/methanol

(from 2% to 3%) as eluent gave 2-(pyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamine (0.24 g, 25%) as an off-white solid.

δ (250 MHz, DMSO): 6.55-6.53 (m, 1H); 6.91 (s, 1H); 7.45 (bs, 2H); 7.56 (dd, $J_1=7.9$ Hz, $J_2=4.9$ Hz, 1H); 7.78 (s, 1H); 8.46-8.41 (m, 1H); 8.72-8.69 (m, 2H); 9.26-9.24 (m, 1H).

5

EXAMPLE 91. *N*-[2-(Pyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide



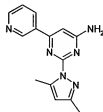
10

Obtained from the title compound of Example 90 (0.14 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent, followed by a second column chromatography with silica gel and methylene chloride/methanol (5%) as eluent gave *N*-[2-(pyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide (54 mg, 31%) as an off-white solid.

δ (250 MHz, DMSO): 1.10 (t, $J=7.4$ Hz, 3H); 2.53 (q, $J=7.4$ Hz, 2H); 6.63 (m, $J_1=2.6$ Hz, $J_2=1.4$ Hz, 1H); 7.65-7.60 (m, 1H); 7.88-7.87 (m, 1H); 8.51 (t, $J=1.4$ Hz, 1H); 8.55 (s, 1H); 8.78 (dd, $J_1=4.6$ Hz, $J_2=1.4$ Hz, 1H); 8.84 (dd, $J_1=2.6$ Hz, $J_2=0.5$ Hz, 1H); 9.35 (d, $J=1.9$ Hz, 1H); 11.36 (s, 1H).

20

EXAMPLE 92. 2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamine



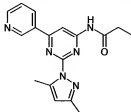
25

Obtained from Intermediate 30 (1.77 g) by the procedure described in Example 76. Purification by column chromatography with silica gel and methylene chloride/methanol (4%) as eluent gave 2-(3,5-dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamine (0.35 g, 8%) as an off-white solid.

δ (250 MHz, CDCl₃): 2.18 (s, 3H); 2.63 (s, 3H); 6.09 (s, 1H); 6.86 (s, 1H); 7.37 (bs, 2H); 7.56 (dd, $J_1=8.0$ Hz, $J_2=4.7$ Hz, 1H); 8.34 (dt, $J_1=8.0$ Hz, $J_2=1.6$ Hz, 1H); 8.69 (dd, $J_1=4.7$ Hz, $J_2=1.6$ Hz, 1H); 9.17 (d, $J=2.2$ Hz, 1H).

35

EXAMPLE 93. *N*-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide



5

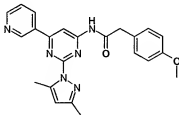
Obtained from the title compound of Example 92 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 2% methanol) as eluent gave *N*-[2-(3,5-dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide (74 mg, 41%) as an off-white solid.

10

δ (250 MHz, CDCl_3): 1.27 (t, $J=7.6$ Hz, 3H); 2.48 (q, $J=7.6$ Hz, 2H); 2.80 (s, 3H); 6.09 (s, 1H); 7.46 (dd, $J_1=8.2$ Hz, $J_2=5.2$ Hz, 1H); 8.40-8.35 (m, 2H); 8.54 (s, 1H); 8.60 (d, $J=2.4$ Hz, 1H); 8.77-8.74 (m, 1H); 9.39-9.38 (m, 1H).

15

EXAMPLE 94. *N*-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide



20

Obtained from the title compound of Example 92 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 5% methanol) as eluent gave *N*-[2-(3,5-dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide (0.20 g, 86%) as an off-white solid.

25

δ (250 MHz, CDCl_3): 2.34 (s, 3H); 2.77 (s, 3H); 3.72 (s, 2H); 3.81 (s, 3H); 6.07 (s, 1H); 6.91 (d, $J=8.8$ Hz, 2H); 7.23 (d, $J=8.8$ Hz, 2H); 7.47-7.42 (m, 1H); 8.40-8.33 (m, 2H); 8.56 (s, 1H); 8.76-8.73 (m, 1H); 9.38-9.36 (m, 1H).

30

Intermediate 31. 3-Amino-3-(pyridin-4-yl)acrylonitrile

Obtained from pyridin-4-carbonitrile (5.00 g) by the procedure described in Intermediate 23 (reaction time: 12 hours). Crystallisation from ethyl ether gave 3-amino-3-(pyridin-4-yl)acrylonitrile, which was used in the next step without further purification.

35

Intermediate 32. 4-Amino-6-(pyridin-4-yl)pyrimidine-2-thiol

Obtained from Intermediate 31 by the procedure described in Intermediate 20. Crystallisation from ethyl ether gave 4-amino-6-(pyridin-4-yl)pyrimidine-2-thiol (7.43 g, global yield: 76%) as a solid, which was used in the next step without further characterisation.

Intermediate 33. 2-Methylsulfonyl-6-(pyridin-4-yl)pyrimidin-4-ylamine

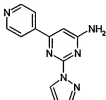
- Obtained from Intermediate 32 (7.00 g) by the procedure described in Intermediate 21.
- 10 Crystallisation from ethyl ether gave the title compound (6.12 g, 82%) as a solid, which was used in the next step without further characterisation.

Intermediate 34. 2-Methanesulfonyl-6-(pyridin-4-yl)pyrimidin-4-ylamine

- Obtained from Intermediate 33 (2.00 g) by the procedure described in Intermediate 22.
- 15 Crystallisation from ethyl ether gave 2-methanesulfonyl-6-(pyridin-4-yl)pyrimidin-4-ylamine (2.29 g, 99%) as a solid, which was used in the next step without further characterisation.

EXAMPLE 95. 2-(Pyrazol-1-yl)-6-(pyridin-4-yl)pyrimidin-4-ylamine

20



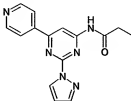
- Obtained from Intermediate 34 (2.00 g) by the procedure described in Example 76.
- 25 Purification by column chromatography with silica gel and methylene chloride/methanol (3%) as eluent gave 2-(pyrazol-1-yl)-6-(pyridin-4-yl)pyrimidin-4-ylamine (0.32 g, 17%) as an off-white solid.

δ (250 MHz, DMSO): 6.56-6.54 (m, 1H); 6.95 (s, 1H); 7.53 (bs, 2H); 7.79-7.78 (m, 1H); 8.02-8.00 (m, 2H); 8.70-8.68 (m, 1H); 8.76-8.74 (m, 2H).

30

EXAMPLE 96. N-[2-(Pyrazol-1-yl)-6-(pyridin-4-yl)pyrimidin-4-yl]propionamide

35



Obtained from the title compound of Example 95 (0.15 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (2%) as eluent gave *N*-[2-(pyrazol-1-yl)-6-(pyridin-4-yl)pyrimidin-4-yl]propionamide (64 mg, 22%) as an off-white solid.

δ (250 MHz, DMSO): 1.10 (t, $J=7.7$ Hz, 3H); 2.53 (q, $J=7.7$ Hz, 2H); 6.65-6.63 (m, 1H); 7.89-7.88 (m, 1H); 8.12-8.10 (m, 2H); 8.59 (s, 1H); 8.83-8.80 (m, 3H); 11.4 (bs, 1H).

Intermediate 35. 3-(Furan-2-yl)-3-oxopropionic acid ethyl ester

To a solution of 60% sodium hydride (95.4 mmol) in diethyl carbonate (90 ml) was slowly added 2-acetylfurane (5.50 g, 45.4 mmol). The resulting solution was stirred at room temperature for 1 hour and at 90°C for 2 hours. The reaction mixture was poured into ice/water and acetic acid (5 mL) was added. The mixture was extracted with ethyl acetate (2x75 mL). The organic layer was washed with water (2x50 mL), brine (50 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. Purification by flash chromatography with silica gel and ethyl acetate/n-hexane (4:1) as eluent gave the title compound (5.90 g, 71%) as a red oil.

δ (200 MHz, CDCl_3): 1.26 (t, $J=7.2$ Hz, 3H); 3.86 (s, 2H); 4.21 (q, $J=7.2$ Hz, 2H); 6.58 (dd, $J_1=3.4$ Hz, $J_2=1.7$ Hz, 1H); 7.28 (d, $J=3.4$ Hz, 1H); 7.62 (d, $J=1.7$ Hz, 1H).

Intermediate 36. 6-(Furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-ol

To a solution of potassium *tert*butoxide (0.87 g, 7.79 mmol) in butanol (3 ml) were added Intermediate 35 (1.00 g, 5.49 mmol) and pyridine-2-carboxamide (HCl) (1.08 g, 6.86 mmol). The mixture was heated at 135°C for 5 hours. The resulting solid was filtered and washed with *n*-pentane. Purification by flash chromatography with silica gel and methylene chloride/methanol (from 1% to 3%) as eluent gave 6-(furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-ol (0.33 g, 25%) as an off-white solid.

δ (200 MHz, CDCl_3): 6.58 (s, 1H); 6.75 (dd, $J_1=3.4$ Hz, $J_2=1.7$ Hz, 1H); 7.39 (d, $J=3.4$ Hz, 1H); 7.66-7.72 (m, 1H); 7.97 (s, 1H); 8.06-8.14 (m, 1H); 8.49 (d, $J=7.7$ Hz, 1H); 8.77 (d, $J=4.7$ Hz, 1H).

Intermediate 37. 4-Chloro-6-(furan-2-yl)-2-(pyridin-2-yl)pyrimidine

Obtained from Intermediate 36 (0.33 g) by the procedure described in Intermediate 10. 4-Chloro-6-(furan-2-yl)-2-(pyridin-2-yl)pyrimidine (0.36 g, 78%) was obtained as a brown solid.

EM (M+): 257.

EXAMPLE 97. 6-(Furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-ylamine

5



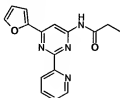
Obtained from Intermediate 37 (0.28 g) by the procedure described in Example 48.

- 10 Purification by column chromatography with silica gel and methylene chloride/methanol (5%) as eluent gave 6-(furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-ylamine (0.16 mg, 62%) as an off-white solid.

δ (300 MHz, CDCl_3): 5.55 (bs, 2H); 6.51 (dd, $J_1=3.4$ Hz, $J_2=1.7$ Hz, 1H); 6.78 (s, 1H); 7.26 (d, $J=3.4$ Hz, 1H); 7.34 (dd, $J_1=8.1$ Hz, $J_2=5.3$ Hz, 1H); 7.52-7.51 (m, 1H); 7.80 (dt, $J_1=7.6$ Hz, $J_2=1.7$ Hz, 1H); 8.50 (d, $J=8.1$ Hz, 1H); 8.77-8.74 (m, 1H).

EXAMPLE 98. N-[6-(Furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-yl]propionamide

20



Obtained from the title compound of Example 97 (0.10 g) by the procedure described in Example 49. Crystallisation from n-pentane gave N-[6-(furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-yl]propionamide (63 mg, 51%) as an off-white solid.

δ (300 MHz, CDCl_3): 1.24 (t, $J=7.5$ Hz, 3H); 2.45 (q, $J=7.5$ Hz, 2H); 6.56 (dd, $J_1=3.4$, $J_2=1.8$ Hz, 1H); 7.36 (d, $J=3.4$ Hz, 1H); 7.43-7.39 (m, 1H); 7.60-7.59 (m, 1H); 7.88 (dt, $J_1=7.6$ Hz, $J_2=1.8$ Hz, 1H); 8.48 (s, 2H); 8.60 (d, $J=8.1$ Hz, 1H); 8.82-8.81 (m, 1H).

30 Intermediate 38. 3-Methylpyridine-2-carboxamide (HCl)

Obtained from 3-methylpyridine-2-carbonitrile (5.15 g) by the procedure described in Intermediate 1. Crystallisation from ethyl ether gave the title compound (3.13 g, 42%) as an off-white solid.

δ (300 MHz, DMSO): 2.41 (s, 3H); 7.56-7.67 (m, 5H); 8.40 (s, 1H); 8.56 (d, $J=3.8$ Hz, 1H).

Intermediate 39. 6-Amino-2-(3-methylpyridin-2-yl)pyrimidin-4-ol

Obtained from Intermediate 38 (2.91 g) by the procedure described in Intermediate

11. Purification by column chromatography with silica gel and methylene chloride
5 /methanol (from 2% to 5%) as eluent gave 6-amino-2-(3-methylpyridin-2-yl)pyrimidin-4-ol
(0.58 g, 17%) as an off-white solid.

δ (300 MHz, DMSO): 2.52 (s, 3H); 5.05 (s, 1H); 6.57 (s, 2H); 7.47 (dd, $J_1=7.6$ Hz, $J_2=4.7$ Hz, 1H); 7.80 (d, $J=7.6$ Hz, 1H); 8.50 (d, $J=4.7$ Hz, 1H); 11.26 (bs, 1H).

10 **Intermediate 40. N-[6-Chloro-2-(3-methylpyridin-2-yl)pyrimidin-4-yl]propionamide**

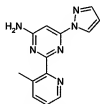
Obtained from Intermediate 39 (0.60 g) by the procedure described in Intermediate

12. Purification by column chromatography with silica gel and methylene chloride
/methanol (5%) as eluent gave N-[6-Chloro-2-(3-methylpyridin-2-yl)pyrimidin-4-yl]
propionamide (0.14 g, 17%) as an off-white solid.

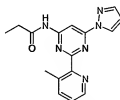
- 15 δ (300 MHz, DMSO): 1.10 (t, $J=7.4$ Hz, 3H); 2.40-2.50 (m, 5H); 7.60 (dd, $J_1=7.6$ Hz, $J_2=4.7$ Hz, 1H); 8.00 (d, $J=7.6$ Hz, 1H); 8.20 (s, 1H); 8.60 (d, $J=4.7$ Hz, 1H); 11.40 (bs, 1H).

EXAMPLES 99 and 100. 2-(3-Methylpyridin-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine

- 20 and N-[2-(3-methylpyridin-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide



Example 99



Example 100

Obtained from Intermediate 40 (0.14 g) by the procedure described in Example 21
(reaction temperature: 110°C). Purification by column chromatography with silica gel and

- 30 methylene chloride/methanol (2%) as eluent 2-(3-methylpyridin-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine (12 mg, 8%) and N-[2-(3-methylpyridin-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl] propionamide (5 mg, 4%) as off-white solids.

Example 99: δ (300 MHz, DMSO): 2.33 (s, 3H); 6.54 (dd, $J_1=2.7$ Hz, $J_2=1.7$ Hz, 1H); 6.91 (s, 1H); 7.31 (bs, 2H); 7.37 (dd, $J_1=7.8$ Hz, $J_2=4.7$ Hz, 1H); 7.74-7.71 (m, 1H); 7.85

(dd, $J_1=1.7$ Hz, $J_2=0.6$ Hz, 1H); 8.38 (bs, 1 H) 8.44 (dd, $J_1=4.7$ Hz, $J_2=1.1$ Hz, 1H); 8.50 (dd, $J_1=2.75$ Hz, $J_2=0.6$ Hz, 1H).

Example 100: δ (300 MHz, DMSO): 1.08 (t, $J=7.6$ Hz, 3H); 2.40 (s, 1H); 2.46 (q, $J=7.6$ Hz, 2H); 6.63 (dd, $J_1=2.8$ Hz, $J_2=1.7$ Hz, 1H); 7.81-7.78 (m, 1H); 7.96-7.94 (m, 1H); 8.51-8.49 (m, 1H); 8.62 (s, 1H); 8.64 (dd, $J_1=2.8$ Hz, $J_2=0.6$ Hz, 1H); 11.24 (bs, 1H).

Intermediate 41. Pyridine-3-carboxamide (HCl)

Obtained from pyridine-3-carbonitrile (10.0 g) by the procedure described in Intermediate 1. Crystallisation from ethyl ether gave the title compound (11.64 g, 99%) as an off-white solid.

δ (200 MHz, DMSO): 7.66-7.70 (m, 1H); 8.23 (d, $J=6.4$ Hz, 1H); 8.80-8.90 (m, 5H); 9.00 (s, 1H).

Intermediate 42. 2-(Pyridin-3-yl)pyrimidine-4,6-diol

Obtained from Intermediate 41 (11.64 g) by the procedure described in Intermediate 2. Crystallisation from ethyl ether gave the title compound (13.68 g, 75%) as an off-white solid.

EM (M⁺): 189.

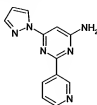
Intermediate 43. 4,6-Dichloro-2-(pyridin-3-yl)pyrimidine

Obtained from Intermediate 42 (12.80 g) by the procedure described in Intermediate 3 (reaction time: 40 hours). Crystallisation from ethyl ether gave 4,6-dichloro-2-(pyridin-3-yl)pyrimidine (6.50 g, 42%) as a solid, which was used in the next step without further characterisation.

Intermediate 44. 6-Chloro-2-(pyridin-3-yl)pyrimidin-4-ylamine

Obtained from Intermediate 43 (2.00 g) by the procedure described in Intermediate 48 (reaction time: 21 hours). Crystallisation from ethyl ether gave 6-chloro-2-(pyridin-3-yl)pyrimidin-4-ylamine (2.14 g, 78%) as a solid, which was used in the next step without further characterisation.

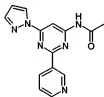
EXAMPLE 101. 6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine



Obtained from Intermediate 44 (1.80 g) by the procedure described in Example 21. Crystallisation from ethyl ether gave 6-(pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine (1.40 g, 67%) as an off-white solid.

δ (250 MHz, DMSO): 6.61-6.59 (m, 1H); 6.89 (s, 1H); 7.35 (bs, 2H); 7.57-7.51 (m, 1H); 7.87-7.86 (m, 1H); 8.71-8.66 (m, 2H); 8.86-8.83 (m, 1H); 9.55-9.53 (m, 1H).

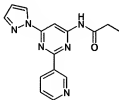
EXAMPLE 102. *N*-[6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]acetamide



Obtained from the title compound of Example 101 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (4%) as eluent gave *N*-[6-(pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]acetamide (80 mg, 23%) as an off-white solid.

δ (250 MHz, CDCl₃): 2.33 (s, 3H); 6.53-6.51 (m, 1H); 7.46-7.40 (m, 1H); 7.83-7.82 (m, 1H); 8.56 (bs, 1H); 8.70-8.64 (m, 3H); 8.75-8.72 (m, 1H); 9.65-9.64 (m, 1H).

EXAMPLE 103. *N*-[6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide



Obtained from the title compound of Example 101 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (4%) as eluent gave *N*-[6-(pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide (0.16 g, 41%) as an off-white solid.

δ (250 MHz, CDCl₃): 1.30 (t, *J*=7.6, 3H); 2.56 (q, *J*=7.6 Hz, 2H); 6.53-6.51 (m, 1H); 7.46-7.40 (m, 1H); 7.82-7.81 (m, 1H); 8.36 (bs, 1H); 8.75-8.64 (m, 4H); 9.64-9.63 (m, 1H).

EXAMPLE 104. 6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine



- 5 Obtained from Intermediate 44 (1.50 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and methylene chloride/methanol (5%) as eluent gave 6-(3,5-dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine (1.25 g, 63%) as an off-white solid.

δ (250 MHz, DMSO): 2.20 (s, 3H); 2.76 (s, 3H); 6.15 (s, 1H); 6.86 (s, 1H); 7.18 (bs, 10 2H); 7.56-7.51 (m, 1H); 8.53-8.52 (m, 1H); 8.69-8.66 (m, 1H); 9.42-9.41 (m, 1H).

EXAMPLE 105. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]acetamide

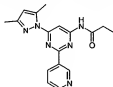


15

- Obtained from the title compound of Example 104 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (4%) as eluent, followed by a second column chromatography with 20 silica gel and ethyl acetate/n-hexane/methanol (85:13:2) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]acetamide (92 mg, 26%) as an off-white solid.

δ (250 MHz, CDCl_3): 2.30 (s, 3H); 2.31 (s, 3H); 2.81 (s, 3H); 6.04 (s, 1H); 7.41 (dd, 17 $J_1=7.9$ Hz, $J_2=4.8$ Hz, 1H); 8.46 (bs, 1H); 8.60-8.55 (m, 2H); 8.71 (dd, $J_1=4.8$ Hz, $J_2=1.5$ 25 Hz, 1H); 9.58-9.56 (m, 1H).

EXAMPLE 106. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide

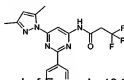


30

- Obtained from the title compound of Example 104 (0.30 g) by the procedure described in Example 2. Purification by column chromatography with silica gel and methylene chloride/methanol (from 4% to 10%) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2- 35 (pyridin-3-yl)pyrimidin-4-yl]propionamide (0.13 g, 34%) as an off-white solid.

δ (250 MHz, CDCl_3): 1.29 (t, $J=7.6$ Hz, 3H); 2.30 (s, 3H); 2.53 (q, $J=7.6$ Hz, 2H); 2.83 (s, 3H); 6.05 (s, 1H); 7.42 (ddd, $J_1=8.1$ Hz, $J_2=4.8$ Hz, 1H); 8.08 (bs, 1H); 8.60 (dt, $J_1=8.1$ Hz, $J_2=2.0$ Hz, 1H); 8.65 (s, 1H); 8.72 (dd, $J_1=4.8$ Hz, $J_2=1.5$ Hz, 1H); 9.59-9.57 (m, 1H).

5 **EXAMPLE 107. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide**



Obtained from the title compound of Example 104 (0.30 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (from 4% to 10%) as eluent gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide (0.11 g, 28%) as an off-white solid.

δ (250 MHz, DMSO): 2.24 (s, 3H); 2.81 (s, 3H); 3.77 (q, $J=10.9$ Hz, 2H); 6.25 (s, 1H); 7.61 (dd, $J_1=7.9$ Hz, $J_2=4.7$ Hz, 1H); 8.47 (s, 1H); 8.60 (dd, $J_1=7.9$ Hz, $J_2=1.4$ Hz, 1H); 8.75 (dd, $J_1=4.7$ Hz, $J_2=1.4$ Hz, 1H); 9.46 (s, 1H); 11.41 (s, 1H).

EXAMPLE 108. 2-(Pyridin-3-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine

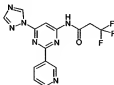


20

Obtained from Intermediate 44 (1.50 g) by the procedure described in Example 21. Purification by column chromatography with silica gel and methylene chloride/methanol (4%) as eluent gave 2-(pyridin-3-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine (0.26 g, 15%) as an off-white solid.

δ (250 MHz, DMSO): 6.83 (s, 1H); 7.57-7.52 (m, 3H); 8.34 (s, 1H); 8.74-8.69 (m, 2H); 9.58-9.57 (m, 1H); 9.67 (s, 1H).

30 **EXAMPLE 109. 3,3,3-Trifluoro-*N*-[2-(pyridin-3-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide**



Obtained from the title compound of Example 108 (0.15 g) by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/methanol (from 4% to 10%) as eluent gave 3,3,3-trifluoro-*N*-[2-(pyridin-3-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl] propionamide (73 mg, 33%) as an off-white solid.

- 5 δ (250 MHz, DMSO): 3.83 (q, $J=10.9$ Hz, 2H); 7.95-7.90 (m, 1H); 8.45 (s, 1H); 8.46 (s, 1H); 8.97-8.93 (m, 1H); 9.10 (d, $J=8.2$ Hz, 1H); 9.74 (bs, 1H); 9.95 (s, 1H); 11.81 (s, 1H).

Intermediate 45. 6-(Furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-ol

- Obtained from Intermediate 35 (1.00 g) and Intermediate 41 (1.08 g) by the procedure described in Intermediate 36. Crystallisation from *n*-pentane gave the title compound (0.27 g, 20%) as a brown solid.

δ (200 MHz, DMSO): 6.26 (s, 1H); 6.64 (d, $J=1.7$ Hz, 1H); 7.12 (d, $J=3.4$ Hz, 1H); 7.44-7.50 (m, 1H); 7.81 (s, 1H); 8.54 (s, 1H); 8.62 (d, $J=4.7$ Hz, 1H); 9.41 (s, 1H).

15 **Intermediate 46. 4-Chloro-6-(furan-2-yl)-2-(pyridin-3-yl)pyrimidine**

Obtained from Intermediate 45 (0.69 g) by the procedure described in Intermediate 10. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 15% methanol) gave the title compound (0.32 g, 43%) as a brown solid, which was used in the next step without further characterisation.

20

EXAMPLE 110. 6-(Furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine



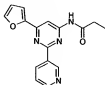
25

Obtained from Intermediate 46 (0.32 g) by the procedure described in Example 48. Purification by column chromatography with silica gel and methylene chloride gave 6-(furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine (80 mg, 27%) as an off-white solid.

- δ (300 MHz, DMSO): 6.69 (dd, $J_1=3.6$ Hz, $J_2=1.9$ Hz, 1H); 6.70 (s, 1H); 7.15 (bs, 2H);
30 7.28 (dd, $J_1=3.3$ Hz, $J_2=0.8$ Hz, 1H); 7.51 (dd, $J_1=8.0$ Hz, $J_2=4.7$ Hz, 1H); 7.89 (dd, $J_1=1.9$ Hz, $J_2=0.8$ Hz, 1H); 8.61 (dt, $J_1=8.0$ Hz, $J_2=1.9$ Hz, 1H); 8.66 (bs, 1H); 9.47 (bs, 1H).

EXAMPLE 111. *N*-[6-(Furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide

35



- 5 Obtained from the title compound of Example 110 (55 mg) by the procedure described in Example 49. Crystallisation from n-pentane gave *N*-[6-(furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide (28 mg, 41%) as an off-white solid.

δ (300 MHz, DMSO): 1.11 (t, $J=7.6$ Hz, 3H); 2.53 (q, $J=7.6$ Hz, 2H); 6.79-6.77 (m, 1H); 7.51 (d, $J=3.6$ Hz, 1H); 7.59 (dd, $J_1=8.5$ Hz, $J_2=4.4$ Hz, 1H); 8.03-8.02 (m, 1H); 8.37 (s, 1H); 8.75-8.68 (m, 2H); 9.57 (d, $J=1.8$ Hz, 1H); 11.01 (s, 1H).

Intermediate 47. 6-Amino-2-(pyridin-4-yl)-pyrimidin-4-ol

- Obtained from pyridine-4-carboxamidine, hydrochloride (2.13 g) by the procedure described in Intermediate 6. Crystallisation from ethyl ether gave the title compound (1.22 g, 48%) as an off-white solid.

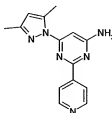
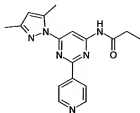
δ (300 MHz, DMSO): 5.27 (s, 1H); 6.70 (s, 2H); 8.00 (d, $J=6.1$ Hz, 2H); 8.71 (d, $J=6.1$ Hz, 2H); 11.74 (bs, 1H).

Intermediate 48. *N*-[6-Chloro-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide

- 20 Obtained from Intermediate 47 (1.22 g) by the procedure described in Intermediate 12. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (from 2:1 to 4:1) as eluent gave impure *N*-[6-Chloro-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide (0.90 g). Purification (0.49 g) by column chromatography with silica gel and chloroform/methanol (3%) as eluent gave the title compound (0.35 g, 38%) as an off-white solid.

δ (200 MHz, ClCD_3): 1.29 (t, $J=7.5$ Hz, 3H); 2.57 (q, $J=7.5$ Hz, 2H); 8.20 (d, $J=6.1$ Hz, 2H); 8.26 (s, 1H); 8.40 (bs, 1H); 8.80 (d, $J=6.1$ Hz, 2H).

- 30 **EXAMPLES 112 and 113. *N*-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide and 6-[3,5-dimethylpyrazol-1-yl]-2-(pyridin-4-yl)pyrimidin-4-ylamine**



Example 112

Example 113

- Obtained from Intermediate 48 (0.17 g) by the procedure described in Example 21 (reaction temperature: 85°C, reaction time: 20 hours). Semi-preparative HPLC purification gave *N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide (19 mg, 9%) and 6-(3,5-dimethylpyrazol-1-yl)-2-(pyridin-4-yl)pyrimidin-4-ylamine (5 mg, 3%) as off-white solids.

- Example 112: δ (300 MHz, CDCl_3): 1.30 (t, $J=7.4$ Hz, 3H); 2.30 (s, 3H); 2.53 (q, $J=7.4$ Hz, 2H); 2.85 (s, 3H); 6.05 (s, 1H); 8.12 (bs, 1H); 8.17 (d, $J=6.1$ Hz, 2H); 8.70 (s, 1H); 8.77 (d, $J=6.1$ Hz, 2H).

- Example 113: δ (300 MHz, CDCl_3): 2.33 (s, 3H); 2.84 (s, 3H); 5.02 (bs, 2H); 6.06 (s, 1H); 7.00 (s, 1H); 8.21-8.19 (m, 2H); 8.76 (bs, 2H).

15 **Intermediate 49. 6-(Furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-ol**

Obtained from Intermediate 35 (1.00 g) by the procedure described in Intermediate 36. Crystallisation from *n*-pentane gave the title compound (0.38 g, 29%) as a brown solid.

- δ (200 MHz, DMSO): 6.74 (dd, $J_1=3.4$ Hz, $J_2=1.7$ Hz, 1H); 7.37 (d, $J=3.4$ Hz, 1H); 7.96 (d, $J=1.7$ Hz, 1H); 8.16 (d, $J=6.4$ Hz, 2H); 8.79 (d, $J=6.4$ Hz, 2H).

20

Intermediate 50. 4-Chloro-6-(furan-2-yl)-2-(pyridin-4-yl)pyrimidine

Obtained from Intermediate 49 (0.63 g) by the procedure described in Intermediate 15 (reaction time: 2 hours). 4-Chloro-6-(furan-2-yl)-2-(pyridin-4-yl)pyrimidine (0.51 g, 76%) was obtained as a brown solid.

- 25 δ (200 MHz, CDCl_3): 6.66-6.68 (m, 1H); 7.49 (d, $J=3.4$ Hz, 1H); 7.65 (d, $J=1.7$ Hz, 1H); 7.68 (s, 1H); 8.44 (d, $J=4.9$ Hz, 2H); 8.83 (d, $J=4.9$ Hz, 2H).

EXAMPLE 114. 6-(Furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-ylamine

30



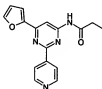
Obtained from Intermediate 50 (0.51 g) by the procedure described in Example 48. Purification by column chromatography with silica gel and methylene chloride/methanol

(from pure methylene chloride to 2% methanol) as eluent gave 6-(furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-ylamine (0.24 g, 51%) as an off-white solid.

δ (300 MHz, CDCl_3): 4.99 (bs, 2H); 6.57-6.55 (m, 1H); 6.75 (s, 1H); 7.28 (d, $J=3.6$ Hz, 1H); 7.55-7.54 (m, 1H); 8.25 (d, $J=6.1$ Hz, 2H); 8.72 (d, $J=6.1$ Hz, 2H).

5

EXAMPLE 115. *N*-[6-(Furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide



10

Obtained from the title compound of Example 114 (0.14 g) by the procedure described in Example 49. Crystallisation from ethyl ether gave *N*-[6-(furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide (0.13 g, 75%) as an off-white solid.

15 δ (300 MHz, DMSO): 1.10 (t, $J=7.6$ Hz, 3H); 2.53 (q, $J=7.6$ Hz, 2H); 6.78 (dd, $J_1=3.4$ Hz, $J_2=1.8$ Hz, 1H); 7.51 (d, $J=3.4$ Hz, 1H); 8.03 (d, $J=2.4$ Hz, 1H); 8.29 (d, $J=6.1$ Hz, 2H); 8.41 (s, 1H); 8.80 (d, $J=6.1$ Hz, 2H); 11.07 (s, 1H).

Intermediate 51. 6-(Furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-ol

20 Obtained from Intermediate 35 (1.00 g) and thiazole-2-carboxamidine (HCl) by the procedure described in Intermediate 36. Purification by column chromatography with silica gel and chloroform/methanol (5%) as eluent gave the title compound (0.40 g, 29%) as an off-white solid.

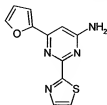
25 δ (300 MHz, CDCl_3): 6.60 (s, 1H); 6.74-6.72 (m, 1H); 7.27-7.24 (m, 1H); 7.97 (s, 1H); 8.15-8.12 (m, 2H).

Intermediate 52. 4-Chloro-6-(furan-2-yl)-2-(thiazol-2-yl)pyrimidine

30 Obtained from Intermediate 51 (0.39 g) by the procedure described in Intermediate 10. Purification by column chromatography with silica gel and methylene chloride as eluent gave 4-chloro-6-(furan-2-yl)-2-(thiazol-2-yl)pyrimidine (0.20 g, 48%) as a pale yellow solid.

δ (300 MHz, CDCl_3): 6.64-6.62 (m, 1H); 7.53-7.51 (m, 1H); 7.59-7.57 (m, 1H); 7.64 (s, 1H); 7.67 (s, 1H); 8.09 (s, 1H).

EXAMPLE 116. 6-(Furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-ylamine

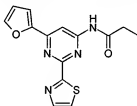


5

Obtained from Intermediate 52 (0.20 g) by the procedure described in Example 48. Purification by column chromatography with silica gel and methylene chloride/ethyl ether (7:3) as eluent gave 6-(furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-ylamine (95 mg, 51%) as an off-white solid.

δ (300 MHz, CDCl_3): 5.22 (bs, 2H); 6.56 (dd, $J_1=3.4$ Hz, $J_2=1.8$ Hz, 1H); 6.76 (s, 1H); 7.32 (dd, $J_1=3.6$ Hz, $J_2=0.8$ Hz, 1H); 7.48 (d, $J=3.0$ Hz, 1H); 7.55 (dd, $J_1=1.8$ Hz, $J_2=0.8$ Hz, 1H); 7.99 (d, $J=3.0$ Hz, 1H).

15 EXAMPLE 117. *N*-[6-(Furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-yl]propionamide



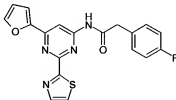
20

Obtained from the title compound of Example 116 (95 mg) by the procedure described in Example 49. by column chromatography with silica gel and ethyl acetate/n-hexane (from 1:1 to pure ethyl acetate) as eluent gave *N*-[6-(furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-yl]propionamide (68 mg, 58%) as an off-white solid.

25 δ (300 MHz, CDCl_3): 1.27 (t, $J=7.4$ Hz, 3H); 2.48 (q, $J=7.4$ Hz, 2H); 6.59 (dd, $J_1=3.6$ Hz, $J_2=1.7$ Hz, 1H); 7.40 (dd, $J_1=3.6$ Hz, $J_2=0.8$ Hz, 1H); 7.53 (d, $J=3.3$ Hz, 1H); 7.63 (dd, $J_1=1.7$ Hz, $J_2=0.8$ Hz, 1H); 8.02 (d, $J=3.3$ Hz, 1H); 8.24 (bs, 1H); 8.47 (s, 1H).

EXAMPLE 118. 2-(4-Fluorophenyl)-*N*-[6-(furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-yl]acetamide

30

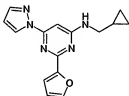


A solution of the title compound of Example 116 (98 mg, 0.4 mmol) and 4-fluorophenylacetyl chloride (164 μ L, 1.20 mmol) in pyridine (6 mL) was heated at 120°C overnight. The solvent was removed under reduced pressure. Methylene chloride was added (20 mL) and the solution was washed with water (2x10mL), brine (10mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure. Purification by column chromatography with silica gel, eluting with ethyl acetate/n-hexane (from pure to 50% of n-hexane), gave 2-(4-fluorophenyl)-N-[6-(furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-yl]acetamide (62 mg, 59%) as an off-white solid.

δ (300 MHz, CDCl₃): 3.74 (s, 2H); 6.58 (dd, $J_1=3.4$ Hz, $J_2=1.8$ Hz, 1H); 7.07 (t, $J=8.6$ Hz, 2H); 7.32-7.27 (m, 2H); 7.38 (dd, $J_1=3.4$ Hz, $J_2=0.8$ Hz, 1H); 7.52 (d, $J=3.0$ Hz, 1H); 7.61 (d, $J=2.8$ Hz, 1H); 8.00 (d, $J=3.0$ Hz, 1H); 8.22 (bs, 1H); 8.46 (s, 1H).

EXAMPLE 119. N-(Cyclopropylmethyl)-2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-amine

15



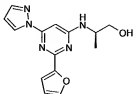
A solution of Intermediate 5 (0.50 g, 2.03 mmol) and cyclopropylmethylamine (0.43 g, 6.08 mmol) in pentanol (12.5 mL) was heated at 100°C overnight. The solvent was removed under reduced pressure. Purification by column chromatography with silica gel, eluting with chloroform, gave N-(cyclopropylmethyl)-2-(2-furyl)-6-(1H-pyrazol-1-yl)pyrimidin-4-amine (0.55 g, 70%) as a solid.

m.p.: 100.9-101.7°C.

δ (300 MHz, CDCl₃): 0.27-0.32 (m, 2H); 0.57-0.63 (m, 2H); 1.06-1.18 (m, 1H); 3.24 (bs, 2H); 5.48 (bs, 1H); 6.47 (dd, $J_1=2.6$ Hz, $J_2=1.6$ Hz, 1H); 6.56 (dd, $J_1=3.3$ Hz, $J_2=1.6$ Hz, 1H); 6.78 (s, 1H); 7.29 (dd, $J_1=3.3$ Hz, $J_2=0.8$ Hz, 1H); 7.61 (dd, $J_1=1.9$ Hz, $J_2=0.8$ Hz, 1H); 7.76 (d, $J=0.8$ Hz, 1H); 8.66 (dd, $J_1=2.6$ Hz, $J_2=0.8$ Hz, 1H).

EXAMPLE 120. (2R)-2-[[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]propan-1-ol

35

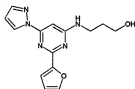


Obtained from Intermediate 5 (100 mg) and (*R*)-2-aminopropanol (189 μ L, 2.43 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 95:5) as eluent gave (2*R*)-2-[[2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]propan-1-ol (88 mg, 76%) as an off-white solid.

m.p.: 163.0-163.8°C.

δ (300 MHz, CDCl_3): 1.32 (d, $J=6.7$ Hz, 3H); 3.65-3.83 (m, 3H); 4.11 (bs, 1H); 5.27 (bs, 1H); 6.47 (dd, $J_1=2.5$ Hz, $J_2=1.7$ Hz, 1H); 6.55 (dd, $J_1=3.3$ Hz, $J_2=1.7$ Hz, 1H); 6.84 (s, 1H); 7.29 (dd, $J_1=3.3$ Hz, $J_2=0.8$ Hz, 1H); 7.61 (dd, $J_1=1.6$ Hz, $J_2=0.8$ Hz, 1H); 7.75 (dd, $J_1=1.6$ Hz, $J_2=0.7$ Hz, 1H); 8.64 (dd, $J_1=2.5$ Hz, $J_2=0.7$ Hz, 1H).

EXAMPLE 121. 3-[[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]propan-1-ol



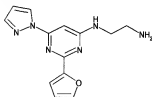
15

Obtained from Intermediate 5 (100 mg) and 3-amino-1-propanol (93 μ L, 1.22 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 95:5) as eluent gave 3-[[2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]propan-1-ol (104 mg, 90%) as an off-white solid.

δ (300 MHz, CDCl_3): 1.80-1.86 (m, 2H); 3.70 (bs, 4H); 5.31 (bs, 1H); 6.47 (dd, $J_1=2.6$ Hz, $J_2=1.6$ Hz, 1H); 6.55 (dd, $J_1=3.5$ Hz, $J_2=1.6$ Hz, 1H); 6.82 (s, 1H); 7.29 (dd, $J_1=3.5$ Hz, $J_2=0.8$ Hz, 1H); 7.61 (dd, $J_1=1.6$ Hz, $J_2=0.8$ Hz, 1H); 7.75 (dd, $J_1=1.6$ Hz, $J_2=0.8$ Hz, 1H) 8.64 (dd, $J_1=2.6$ Hz, $J_2=0.8$ Hz, 1H).

25

EXAMPLE 122. N-[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]ethane-1,2-diamine



30

The precursor intermediate *tert*-butyl 2-[[2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]ethylcarbamate was obtained from Intermediate 5 (145 mg) and N-BOC-

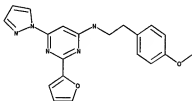
35

ethylenediamine (279 μ L, 1.76 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 95:5) as eluent gave 351 mg, (80%) of the intermediate.

- 5 To a solution of the intermediate *tert*-butyl 2-[[2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]ethylcarbamate (0.28 g, 0.76 mmol) in chloroform (1.7 mL) was added trifluoroacetic acid (0.58 mL, 7.56 mmol). The mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. To the residue was added water (25 mL), potassium carbonate until basic pH, and methylene chloride (2x20 mL).
- 10 The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. Crystallisation of the residue obtained in ethyl ether/diisopropyl ether (1:1) gave *N*-[2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]ethane-1,2-diamine (77 mg, 38%) as an off white solid. m.p.: 104.1-105.1°C.
- δ (300 MHz, CDCl_3): 2.99-3.03 (t, J =5.9 Hz, 2H); 3.46-3.50 (m, 2H); 5.69 (bs, 1H); 6.47 (dd, J_1 =2.6 Hz, J_2 =1.6 Hz, 1H); 6.55 (dd, J_1 =3.4 Hz, J_2 =1.8 Hz, 1H); 6.83 (s, 1H); 7.29 (d, J =3.3 Hz, 1H) 7.60-7.61 (m, 1H); 7.75-7.76 (m, 1H); 8.65 (d, J =2.6 Hz, 1H).

EXAMPLE 123. 2-(2-Furyl)-*N*-[2-(4-methoxyphenyl)ethyl]-6-(pyrazol-1-yl)pyrimidin-4-amine

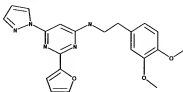
20



- Obtained from Intermediate 5 (100 mg) and (4-methoxyphenyl)ethylamine (177 μ L, 1.22 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and *n*-hexane/ethyl acetate (from 10:1 to 2:1) as eluent gave 2-(2-furyl)-*N*-[2-(4-methoxyphenyl)ethyl]-6-(pyrazol-1-yl)pyrimidin-4-amine (111 mg, 76%) as an oil.
- δ (300 MHz, CDCl_3): 2.92 (t, J =7.0 Hz, 2H); 3.65 (bs, 2H); 3.80 (s, 3H); 5.28 (bs, 1H); 6.47 (dd, J_1 =2.5 Hz, J_2 =1.7 Hz, 1H); 6.55 (dd, J_1 =3.3 Hz, J_2 =1.7 Hz, 1H); 6.80 (s, 1H); 6.85-6.88 (m, 2H); 7.15-7.18 (m, 2H); 7.29 (dd, J =3.3 Hz, J_2 =0.7 Hz, 1H); 7.59-7.60 (m, 1H); 7.76 (d, J =1.1 Hz, 1H); 8.65 (dd, J_1 =2.6 Hz, J_2 =0.7 Hz, 1H).

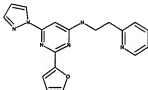
EXAMPLE 124. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-amine

35



- 5 Obtained from Intermediate 5 (100 mg) and (3,4-dimethoxyphenyl)ethylamine (177 μ L, 1.22 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 99:1) as eluent gave *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-amine (77 mg, 49%) as an oil.
- 10 δ (300 MHz, CDCl_3): 2.92 (t, J =7.0 Hz, 2H); 3.67 (bs, 2H); 3.87 (s, 3H); 3.88 (s, 3H); 5.30 (bs, 1H); 6.47 (dd, J_1 =2.5 Hz, J_2 =1.7 Hz, 1H); 6.55 (dd, J_1 =3.3 Hz, J_2 =1.7 Hz, 1H); 6.75-6.76 (m, 1H); 6.80-6.82 (m, 3H); 7.29 (dd, J_1 =3.3 Hz, J_2 =0.9 Hz, 1H); 7.60 (dd, J_1 =1.7 Hz, J_2 =0.9 Hz, 1H); 7.75-7.77 (m, 1H); 8.65 (dd, J =2.6 Hz, J_2 =0.7 Hz, 1H).

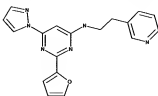
15 **EXAMPLE 125. 2-(2-Furyl)-6-(pyrazol-1-yl)-*N*-[2-(pyridin-2-yl)ethyl]pyrimidin-4-amine**



- 20 Obtained from Intermediate 5 (100 mg) and 2-(2-aminoethyl)pyridine (145 μ L, 1.22 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene chloride to 8:2) as eluent gave 2-(2-furyl)-6-(pyrazol-1-yl)-*N*-[2-(pyridin-2-yl)ethyl]pyrimidin-4-amine (86 mg, 64%) as an off-white solid.
- 25 m.p.: 110.2-110.9°C.
- δ (300 MHz, CDCl_3): 3.14 (t, J =6.5 Hz, 2H); 3.88 (bs, 2H); 5.95 (bs, 1H); 6.47 (dd, J_1 =2.5 Hz, J_2 =1.7 Hz, 1H); 6.55 (dd, J_1 =3.3 Hz, J_2 =1.7 Hz, 1H); 6.84 (s, 1H); 7.14-7.20 (m, 2H); 7.29 (dd, J_1 =3.3 Hz, J_2 =0.8 Hz, 1H); 7.59-7.65 (m, 2H); 7.75-7.76 (m, 1H); 8.56-8.59 (m, 1H); 8.65 (dd, J_1 =2.5 Hz, J_2 =0.8 Hz, 1H).

30

EXAMPLE 126. 2-(2-Furyl)-6-(pyrazol-1-yl)-*N*-[2-(pyridin-3-yl)ethyl]pyrimidin-4-amine



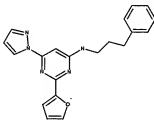
Obtained from Intermediate 5 (100 mg) and 3-(2-aminoethyl)pyridine (149 mg, 1.22 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and chloroform/methanol (from pure chloroform to 100:1) as eluent gave 2-(2-furyl)-6-(pyrazol-1-yl)-N-[2-(pyridin-3-yl)ethyl]pyrimidin-4-amine (94 mg, 70%) as an off-white solid.

m.p.: 164.0-164.9°C.

δ (300 MHz, CDCl_3): 3.00 (t, $J=6.9$ Hz, 2H); 3.71-3.75 (m, 2H); 5.30 (s, 1H); 6.48 (s, 1H); 6.55-6.56 (m, 1H); 6.82 (s, 1H); 7.24-7.30 (m, 3H); 7.57-7.60 (m, 2H); 7.76 (s, 1H); 8.50-8.53 (m, 2H); 8.65-8.66 (m, 1H).

EXAMPLE 127. 2-(2-Furyl)-N-(3-phenylpropyl)-6-(pyrazol-1-yl)pyrimidin-4-amine

15

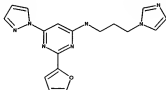


Obtained from Intermediate 5 (100 mg) and 3-phenylpropylamine (173 μL , 1.22 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and n-hexane/ethyl acetate (from 10:1 to 2:1) as eluent gave 2-(2-furyl)-N-(3-phenylpropyl)-6-(pyrazol-1-yl)pyrimidin-4-amine (124 mg, 89%) as an off-white solid.

δ (300 MHz, CDCl_3): 2.01 (q, $J=7.5$ Hz, 2H); 2.76 (t, $J=7.5$ Hz, 2H); 3.41 (bs, 2H); 5.34 (bs, 1H); 6.47 (dd, $J_1=2.5$ Hz, $J_2=1.7$ Hz, 1H); 6.56 (dd, $J_1=3.3$ Hz, $J_2=1.7$ Hz, 1H); 6.77 (s, 1H); 7.19-7.31 (m, 6H); 7.61 (s, 1H); 7.76 (s, 1H); 8.65-8.66 (m, 1H)

EXAMPLE 128. 2-(2-Furyl)-N-[3-(imidazol-1-yl)propyl]-6-(pyrazol-1-yl)pyrimidin-4-amine

30



Obtained from Intermediate 5 (100 mg) and 3-(imidazol-1-yl)propylamine (145 μL , 1.22 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and methylene chloride/methanol (from pure methylene

chloride to 97:3) as eluent gave 2-(2-furyl)-*N*-[3-(imidazol-1-yl)propyl]-6-(pyrazol-1-yl)pyrimidin-4-amine (122 mg, 90%) as an off-white solid.

- δ (300 MHz, CDCl_3): 2.18 (q, $J=6.7$ Hz, 2H); 3.43-3.50 (m, 2H); 4.11 (t, $J=6.7$ Hz, 2H); 5.26 (bs, 1H); 6.49 (dd, $J_1=2.6$ Hz, $J_2=1.7$ Hz, 1H); 6.58 (dd, $J_1=3.3$ Hz, $J_2=1.7$ Hz, 1H); 6.79 (s, 1H); 6.97-6.98 (m, 1H); 7.10-7.11 (m, 1H); 7.30 (dd, $J_1=3.3$ Hz, $J_2=0.8$ Hz, 1H); 7.54 (bs, 1H); 7.63 (dd, $J_1=1.7$ Hz, $J_2=0.8$ Hz, 1H) 7.76-7.77 (dd, $J_1=1.7$ Hz, $J_2=0.8$ Hz, 1H); 8.66 (dd, $J_1=2.6$ Hz, $J_2=0.8$ Hz, 1H).

Intermediate 53. 2-(Thiophen-2-yl)pyrimidine-4,6-diol

- Obtained from Intermediate 13 (1.35 g) by the procedure described in Intermediate 2. Crystallisation from diisopropyl ether gave 2-(thiophen-2-yl)pyrimidine-4,6-diol (0.44 g, 34%) as a pale yellow solid.

δ (300 MHz, DMSO): 5.15 (s, 1H); 7.07-7.19 (m, 1H); 7.72-7.78 (m, 1H); 8.00-8.02 (m, 1H).

Intermediate 54. 4,6-Dichloro-2-(thiophen-2-yl)pyrimidine

Obtained from Intermediate 53 (0.44 g) by the procedure described in Intermediate 3. Crystallisation from diisopropyl ether gave 4,6-dichloro-2-(thiophen-2-yl)pyrimidine (0.41 g, 78%) as a brown solid.

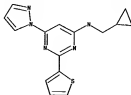
- δ (300 MHz, CDCl_3): 7.12-7.20 (m, 2H); 7.54-7.60 (m, 1H); 8.05-8.08 (m, 1H).

Intermediate 55. 4-Chloro-6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidine

Obtained from Intermediate 54 (0.69 g) by the procedure described in Intermediate 5. Purification by column chromatography with silica gel and n-hexane/ethyl acetate (from pure n-hexane to 3:1) as eluent gave 4-chloro-6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidine (0.49 g, 68%) as an off-white solid.

δ (300 MHz, CDCl_3): 6.56 (s, 1H); 7.16-7.20 (m, 1H); 7.54-7.58 (m, 1H); 7.75 (s, 1H); 7.84 (s, 1H); 8.08-8.11 (m, 1H); 8.68 (s 1H).

- EXAMPLE 129. *N*-(Cyclopropylmethyl)-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine**



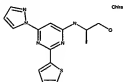
Obtained from Intermediate 55 (100 mg) and cyclopropylmethylamine (99 μ L, 1.14 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and n-hexane/ethyl acetate (from 95:5 to 90:10) as eluent gave N-(cyclopropylmethyl)-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine (98 mg, 87%)

5 as an off-white solid.

m.p.: 134.6-135.3°C.

δ (300 MHz, CDCl_3): 0.31 (m, 2H); 0.60 (m, 2H); 1.08-1.18 (m, 1H); 3.27 (bs, 2H); 5.32 (bs, 1H); 6.47 (dd, $J_1=2.5$ Hz, $J_2=1.7$ Hz, 1H); 6.76 (s, 1H); 7.13 (dd, $J_1=4.9$ Hz, $J_2=3.6$ Hz, 1H); 7.44 (dd, $J_1=4.9$ Hz, $J_2=1.2$ Hz, 1H); 7.75 (bs, 1H); 7.97 (d, $J_1=3.6$ Hz, $J_2=1.2$ Hz, 1H); 8.67 (d, $J=2.2$ Hz, 1H).

EXAMPLE 130. (2R)-2-[[6-(Pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amino]propan-1-ol



15

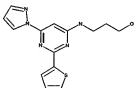
Obtained from Intermediate 55 (100 mg) and (R)-2-aminopropanol (177 μ L, 2.28 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and n-hexane/ethyl acetate (from pure n-hexane to 3:2) as eluent gave (2R)-2-[[6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amino]propan-1-ol (87 mg, 76%) as an off-white solid.

m.p.: 135.7-136.9°C.

δ (300 MHz, CDCl_3): 1.33 (d, $J=6.9$ Hz, 3H); 3.66-3.72 (m, 1H); 3.81-3.87 (m, 1H); 4.23 (bs, 1H); 5.15 (bs, 1H); 6.48-6.49 (m, 1H); 6.82 (s, 1H); 7.14 (dd, $J_1=5.1$ Hz, $J_2=3.7$ Hz, 1H); 7.46 (dd, $J_1=5.1$ Hz, $J_2=1.2$ Hz, 1H); 7.76 (m, 1H); 7.97 (dd, $J_1=3.7$ Hz, $J_2=1.2$ Hz, 1H); 8.66 (dd, $J_1=2.7$ Hz, $J_2=1.9$ Hz, 1H).

25

EXAMPLE 131. 3-[[6-(Pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amino]propan-1-ol



30

Obtained from Intermediate 55 (100 mg) and 3-amino-1-propanol (87 μ L, 1.14 mmol) by the procedure described in Example 119. Purification by column chromatography with

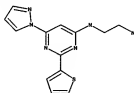
35

silica gel and n-hexane/ethyl acetate (from pure n-hexane to 3:2) as eluent gave 3-[[6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amino]propan-1-ol (94 mg, 82%) as an off-white solid.

m.p.: 129.9-130.8°C.

- 5 δ (300 MHz, CDCl_3): 1.87 (q, $J=6.0$ Hz, 2H); 3.73 (bs, 5H); 5.30 (s, 1H); 6.47 (dd, $J_1=2.6$ Hz, $J_2=1.7$ Hz, 1H); 6.79 (s, 1H); 7.13 (dd, $J_1=4.9$ Hz, $J_2=3.6$ Hz, 1H); 7.45 (dd, $J_1=4.9$ Hz, $J_2=1.2$ Hz, 1H); 7.75 (dd, $J_1=1.7$ Hz, $J_2=0.8$ Hz, 1H); 7.96 (dd, $J_1=3.6$ Hz, $J_2=1.2$ Hz, 1H); 8.65 (dd, $J_1=2.6$ Hz, $J_2=0.8$ Hz, 1H).

10 **EXAMPLE 132. *N*-(2-Aminoethyl)-*N*-[6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amine**



15

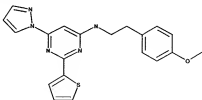
The intermediate *tert*-butyl 2-[[2-(2-thienyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]ethylcarbamate was obtained from Intermediate 55 (100 mg) and *N*-BOC-ethylenediamine (180 μL , 1.14 mmol) by the synthetic procedure described in Example 122.

- 20 Purification of the final product by column chromatography with silica gel and methylene chloride/methanol/ NH_4OH (95:2.5:2.5) as eluent gave *N*-(2-Aminoethyl)-*N*-[6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amine (86 mg, (47%) as a solid.

m.p.: 146.6-147.1°C.

- 25 δ (300 MHz, CDCl_3): .01 (t, $J=5.8$ Hz, 2H); 3.50 (bs, 2H); 5.59 (bs, 1H); 6.46-6.48 (m, 1H); 6.80 (s, 1H); 7.11-7.15 (m, 1H); 7.45 (dt, $J_1=4.9$ Hz, $J_2=1.1$ Hz, 1H); 7.75-7.76 (m, 1H); 7.97 (dd, $J_1=3.7$ Hz, $J_2=1.1$ Hz, 1H); 8.66 (d, $J=2.7$ Hz, 1H).

30 **EXAMPLE 133. *N*-[2-(4-Methoxyphenyl)ethyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine**



30

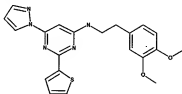
- 35 Obtained from Intermediate 55 (100 mg) and (4-methoxyphenyl)ethylamine (166 μL , 1.14 mmol) by the procedure described in Example 119. Purification by column

chromatography with silica gel and n-hexane/ethyl acetate (from pure n-hexane to 4:1) as eluent gave *N*-[2-(4-methoxyphenyl)ethyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine (121 mg, 84%) as an off-white solid.

m.p.: 99.6-100.4°C.

- 5 δ (300 MHz, CDCl_3): 2.92 (t, $J=7.0$ Hz, 2H); 3.67 (bs, 2H); 3.81 (m, 3H); 5.12 (bs, 1H); 6.47 (dd, $J_1=2.6$ Hz, $J_2=1.7$ Hz, 1H); 6.87 (dt, $J_1=4.4$ Hz, $J_2=2.6$ Hz, 2H); 7.11-7.26 (m, 3H); 7.45 (dd, $J_1=4.9$ Hz, $J_2=1.4$ Hz, 1H); 7.75 (d, $J=0.8$ Hz, 1H); 7.98 (dd, $J_1=3.6$ Hz, $J_2=1.1$ Hz, 1H); 8.66 (dd, $J_1=2.6$ Hz, $J_2=0.8$ Hz, 1H).

10 **EXAMPLE 134. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine**

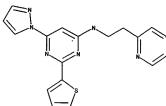


15

Obtained from Intermediate 55 (100 mg) and (3,4-dimethoxyphenyl)ethylamine (192 μL , 1.14 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and n-hexane/ethyl acetate (from 85:15 to 70:30) as eluent gave *N*-[2-(3,4-dimethoxyphenyl)ethyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine (117 mg, 76%) as an oil.

- 20 m.p.: 116.2-117.3°C.
- 25 δ (300 MHz, CDCl_3): 2.93 (t, $J=7.0$ Hz, 2H); 3.70 (bs, 2H); 3.88 (s, 3H); 3.89 (m, 3H); 5.16 (bs, 1H); 6.47 (dd, $J_1=2.6$ Hz, $J_2=1.7$ Hz, 1H); 6.77-6.85 (m, 4H); 7.13 (dd, $J_1=4.9$ Hz, $J_2=3.6$ Hz, 1H); 7.45 (dd, $J_1=4.9$ Hz, $J_2=1.4$ Hz, 1H); 7.75 (d, $J=0.8$ Hz, 1H); 7.98 (dd, $J_1=3.6$ Hz, $J_2=1.1$ Hz, 1H); 8.66 (dd, $J_1=2.6$ Hz, $J_2=0.8$ Hz, 1H).

EXAMPLE 135. 6-(Pyrazol-1-yl)-*N*-[2-(pyridin-2-yl)ethyl]-2-(thien-2-yl)pyrimidin-4-amine



30

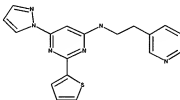
Obtained from Intermediate 55 (100 mg) and 2-(2-aminoethyl)pyridine (137 μL , 1.22 mmol) by the procedure described in Example 119. Purification by column

chromatography with silica gel and n-hexane/ethyl acetate (from pure n-hexane to 2:3) as eluent gave 6-(pyrazol-1-yl)-*N*-[2-(pyridin-2-yl)ethyl]-2-(thien-2-yl)pyrimidin-4-amine (58 mg, 44%) as an off-white solid.

m.p.: 132.9-133.6°C.

- 5 δ (300 MHz, CDCl_3): 3.16 (t, $J=6.5$ Hz, 2H); 3.90 (bs, 2H); 5.88 (t, $J=5.2$ Hz, 1H); 6.46 (dd, $J_1=2.6$ Hz, $J_2=1.6$ Hz, 1H); 6.79 (s, 1H); 7.11-7.21 (m, 3H); 7.44 (dd, $J_1=5.1$ Hz, $J_2=1.2$ Hz, 1H); 7.63 (dt, $J_1=7.7$ Hz, $J_2=1.9$ Hz, 1H); 7.74-7.75 (m, 1H); 7.98 (dd, $J_1=3.6$ Hz, $J_2=0.7$ Hz, 1H) 8.58 (m, 1 H) 8.65 (dd, $J_1=2.6$ Hz, $J_2=0.7$ Hz, 1H).

10 **EXAMPLE 136. 6-(Pyrazol-1-yl)-*N*-[2-(pyridin-3-yl)ethyl]-2-(thien-2-yl)pyrimidin-4-amine**



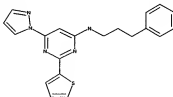
15

Obtained from Intermediate 55 (100 mg) and 3-(2-aminoethyl)pyridine (139 mg, 1.14 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and n-hexane/ethyl acetate (from 1:1 to pure ethyl acetate) as eluent gave 6-(pyrazol-1-yl)-*N*-[2-(pyridin-3-yl)ethyl]-2-(thien-2-yl)pyrimidin-4-amine (106 mg, 80%) as an off-white solid.

m.p.: 159.0-160.5°C.

- 20 δ (300 MHz, CDCl_3): 3.02 (t, $J=7.14$ Hz, 2 H) 3.75 (m, 2 H) 5.16 (s, 1 H) 6.48 (m, $J=2.75$, 1.65 Hz, 1 H) 6.78 (s, 1 H) 7.14 (dd, $J=5.08$, 3.71 Hz, 1 H) 7.25 (dd, $J=4.53$, 0.69 Hz, 1 H) 7.28 (dd, $J=4.81$, 0.69 Hz, 1 H) 7.47 (dd, $J=4.94$, 1.37 Hz, 1 H) 7.59 (m, $J=7.69$, 1.65, 0.55 Hz, 1 H) 7.75 (dd, $J=1.51$, 0.69 Hz, 1 H) 7.99 (dd, $J=3.71$, 1.24 Hz, 1 H) 8.51 (dd, $J=4.67$, 1.65 Hz, 1 H) 8.55 (d, $J=1.65$ Hz, 1 H) 8.67 (dd, $J=2.75$, 0.82 Hz, 1 H)

EXAMPLE 137. *N*-(3-Phenylpropyl)-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine



30

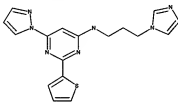
Obtained from Intermediate 55 (100 mg) and 3-phenylpropylamine (162 μL , 1.14 mmol) by the procedure described in Example 119. Purification by column chromatography with

silica gel and n-hexane/ethyl acetate (from 95:5 to 90:10) as eluent gave *N*-(3-phenylpropyl)-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine (98 mg, 72%) as an off-white solid.

m.p.: 83.6-84.5°C.

- 5 δ (300 MHz, CDCl_3): 2.02 (q, $J=7.4$ Hz, 2H); 2.76 (t, $J=7.4$ Hz, 2H); 3.44 (bs, 2H); 5.17 (bs, 1H); 6.47 (dd, $J_1=2.7$ Hz, $J_2=1.7$ Hz, 1H); 6.74 (s, 1H); 7.22-7.31 (m, 6H); 7.45 (dd, $J_1=5.1$ Hz, $J_2=1.2$ Hz, 1H); 7.75 (dd, $J_1=1.7$ Hz, $J_2=0.6$ Hz, 1H); 7.95 (dd, $J_1=3.7$ Hz, $J_2=1.2$ Hz, 1H); 8.66 (dd, $J_1=2.7$ Hz, $J_2=0.6$ Hz, 1H).

10 **EXAMPLE 138.** *N*-[3-(imidazol-1-yl)propyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine



15

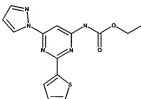
Obtained from Intermediate 5 (100 mg) and 3-(imidazol-1-yl)propylamine (136 μL , 1.14 mmol) by the procedure described in Example 119. Purification by column chromatography with silica gel and methylene chloride/methanol (97:3) as eluent gave *N*-[3-(imidazol-1-yl)propyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine (130 mg, 98%) as an off-white solid.

20

δ (300 MHz, CDCl_3): 2.20 (q, $J=7.0$ Hz, 2H); 3.46-3.54 (m, 2H); 4.11 (t, $J=7.0$ Hz, 2H); 5.14 (bs, 1H); 6.48 (dd, $J_1=2.7$ Hz, $J_2=1.7$ Hz, 1H); 6.77 (s, 1H); 6.97 (t, $J=1.2$ Hz, 1H); 7.10 (t, $J=1.2$ Hz, 1H); 7.14 (dd, $J_1=5.1$ Hz, $J_2=3.7$ Hz, 1H); 7.47 (dd, $J_1=5.1$ Hz, $J_2=1.2$ Hz, 1H); 7.54 (s, 1H); 7.75 (dd, $J_1=1.5$ Hz, $J_2=0.7$ Hz, 1 H) 7.97 (dd, $J_1=3.7$ Hz, $J_2=1.2$ Hz, 1H); 8.66 (dd, $J_1=2.7$ Hz, $J_2=0.7$ Hz, 1H).

25

EXAMPLE 139. Ethyl 6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-ylcarbamate



30

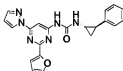
A solution of the title compound of Example 56 (0.37 g, 1.52 mmol), diethyl pyrocarbonate (246 μL , 1.67 mmol) and dimethylaminopyridine (50 mg, 0.41 mmol) in tetrahydrofuran (4 mL) was heated at 45°C overnight. The reaction was poured into water

35

(40 mL) and extracted with ethyl acetate (2x25 mL). The organic phase was washed with water (2x25 mL), brine (25 mL), dried (Na₂SO₄), and the solvent was removed under reduced pressure. Purification by column chromatography with silica gel, eluting with n-hexane/ethyl acetate (9:1) as eluent gave ethyl 6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-ylcarbamate (34 mg, 7%) as an off-white solid.

δ (300 MHz, CDCl₃): 1.35 (t, J =7.0 Hz, 3H); 4.31 (d, J =7.0 Hz, 2H); 6.50 (dd, J_1 =2.6 Hz, J_2 =1.2 Hz, 1H); 7.15 (dd, J_1 =5.1 Hz, J_2 =3.7 Hz, 1H); 7.49 (dd, J_1 =5.1 Hz, J_2 =1.6 Hz, 1H); 7.52 (bs, 1H); 7.80 (dd, J_1 =1.6 Hz, J_2 =0.7 Hz, 1H); 7.99 (dd, J_1 =3.7 Hz, J_2 =1.2 Hz, 1H); 8.33 (s, 1H); 8.66 (dd, J_1 =2.6 Hz, J_2 =0.7 Hz, 1H).

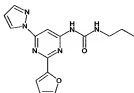
EXAMPLE 140. 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(2-phenylcyclopropyl)urea



To a cooled solution (-78°C) of the title compound of Example 1 (0.22 g, 0.97 mmol) in anhydrous THF (14 mL) was slowly added 2.5M n-butyllithium in hexane (0.78 mL). The mixture was stirred at -78°C for 1 hour and then, a solution of phenylcyclopropylisocyanate (0.22 mg, 1.40 mmol) in anhydrous THF (2 mL) was slowly added. The mixture was allowed to stand at room temperature for 2 hours. Water (15 mL) was added and the organic phase was diluted with ethyl acetate (20 mL). The organic layer was washed with brine (2x20 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. Purification by column chromatography with silica gel, eluting with methylene chloride/methanol (99:1) as eluent, followed by a semi-preparative HPLC purification gave 1-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(2-phenylcyclopropyl)urea (150 mg, 40%) as an off-white solid.

δ (400 MHz, DMSO): 1.18-1.32 (m, 1H); 2.05-2.12 (m, 1H); 2.81-2.88 (m, 1H); 6.64 (s, 1H); 6.76 (dd, J_1 =3.3 Hz, J_2 =1.8 Hz, 1H); 7.14-7.22 (m, 3H); 7.26-7.31 (m, 2H); 7.44 (d, J =3.1 Hz, 1H); 7.89 (s, 1H); 7.91 (s, 1 H); 7.98 (s, 1H); 8.10 (bs, 1H); 8.75 (d, J =2.3 Hz, 1H); 9.96 (bs, 1H).

EXAMPLE 141. 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-propylurea

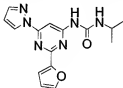


Obtained from the title compound of Example 1 (0.22 g) and propylisocyanate (0.12 g, 1.40 mmol) by the procedure described in Example 140. Purification by column chromatography with silica gel and methylene chloride/methanol (99:1) as eluent gave 1-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-propylurea (68 mg, 20%) as an off-white solid.

δ (300 MHz, DMSO): 0.94 (t, $J=7.4$ Hz, 3H); 1.53 (h, $J=7.4$ Hz, 2 H); 3.18 (q, $J=7.4$ Hz, 2H); 6.65 (dd, $J_1=2.7$ Hz, $J_2=1.7$ Hz, 1H); 6.75 (dd, $J_1=3.4$ Hz, $J_2=1.7$ Hz, 1H); 7.44 (dd, $J_1=3.4$ Hz, $J_2=0.8$ Hz, 1H); 7.86 (bs, 1H); 7.92 (dd, $J_1=1.7$ Hz, $J_2=0.7$ Hz, 1H); 7.96 (dd, $J_1=1.7$ Hz, $J_2=0.8$ Hz, 1H); 8.75 (dd, $J_1=2.7$ Hz, $J_2=0.7$ Hz, 1H); 9.97 (bs, 1H).

EXAMPLE 142. 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-isopropylurea

15

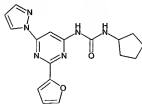


Obtained from the title compound of Example 1 (0.22 g) and isopropylisocyanate (0.12 g, 1.40 mmol) by the procedure described in Example 140. Purification by column chromatography with silica gel and methylene chloride/methanol (99:1) as eluent gave 1-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-isopropylurea (147 mg, 48%) as an off-white solid.

δ (400 MHz, DMSO): 1.19 (d, $J=6.7$ Hz, 6H); 3.84 (h, $J=6.7$ Hz, 1H); 6.64 (s, 1H); 6.75 (s, 1H); 7.42 (d, $J=3.1$ Hz, 1H); 7.80 (s, 1H); 7.92 (s, 1H); 7.97 (s, 1H); 8.75 (d, $J=2.3$ Hz, 1H); 9.87 (s, 1 H).

EXAMPLE 143. 1-Cyclopentyl-3-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]urea

30

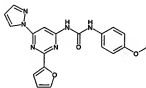


Obtained from the title compound of Example 1 (0.22 g) and cyclopentylisocyanate (0.16 g, 1.40 mmol) by the procedure described in Example 140. Purification by column

chromatography with silica gel and methylene chloride/methanol (99:1) as eluent gave 1-cyclopentyl-3-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]urea (125 mg, 38%) as an off-white solid.

- δ (300 MHz, DMSO): 1.42-1.54 (m, 2H); 1.55-1.66 (m, 2H); 1.67-1.75 (m, 2H); 1.84-1.96 (m, 2H); 3.99-4.09 (m, 1H); 6.65 (dd, $J_1=2.7$ Hz, $J_2=1.6$ Hz, 1H); 6.76 (dd, $J_1=3.4$ Hz, $J_2=1.6$ Hz, 1H); 7.43 (d, $J=2.7$ Hz, 1H); 7.76 (s, 1H); 7.92 (d, $J=1.1$ Hz, 1H); 7.97 (s, 1H); 8.10 (bs, 1H); 8.75 (d, $J=2.7$ Hz, 1H); 9.89 (s, 1H).

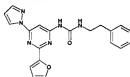
EXAMPLE 144. 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(4-methoxyphenyl)urea



- Obtained from the title compound of Example 1 (0.22 g) and 4-methoxybenzeneisocyanate (0.21 g, 1.40 mmol) by the procedure described in Example 140. Purification by column chromatography with silica gel and methylene chloride/methanol (98:2) as eluent gave 1-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(4-methoxyphenyl)urea (82 mg, 22%) as an off-white solid.

- δ (400 MHz, DMSO): 3.75 (s, 3H); 6.66 (dd, $J_1=2.7$ Hz, $J_2=1.8$ Hz, 1H); 6.78 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 6.93-7.0 (m, 2H); 7.46-7.52 (m, 3H); 7.89 (s, 1H); 7.94 (s, 1H); 8.03 (s, 1H); 8.78 (d, $J=2.7$ Hz, 1H); 10.13 (s, 1H); 10.17 (bs, 1H).

EXAMPLE 145. 1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenethylurea



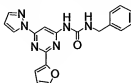
- Obtained from the title compound of Example 1 (0.22 g) and phenethylisocyanate (0.21 g, 1.40 mmol) by the procedure described in Example 140. Purification by column chromatography with silica gel and methylene chloride/methanol (99:1) as eluent gave 1-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenethylurea (35 mg, 10%) as an off-white solid.

- δ (400 MHz, DMSO): 2.83 (t, $J=7.0$ Hz, 2H); 3.47 (q, $J=7.0$ Hz, 2H); 6.64 (dd, $J_1=2.7$ Hz, $J_2=1.6$ Hz, 1H); 6.72 (dd, $J_1=3.3$ Hz, $J_2=1.8$ Hz, 1H); 7.18-7.24 (m, 1H); 7.26-7.34

(m, 5H); 7.64 (bs, 1H); 7.90-7.92 (m, 2H); 7.93-7.95 (m, 1H); 8.73 (d, $J=2.7$ Hz, 1H); 9.98 (bs, 1H).

EXAMPLE 146. 1-Benzyl-3-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]urea

5



10 Obtained from the title compound of Example 1 (0.22 g) and benzylisocyanate (0.19 g, 1.40 mmol) by the procedure described in Example 140. Purification by column chromatography with silica gel and methylene chloride/methanol (from 99:1 to 85:5) as eluent, followed by a semi-preparative HPLC purification gave 1-benzyl-3-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]urea (10 mg, 3%) as an off-white solid.

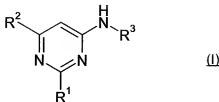
EM (M^+): 360.

15

CLAIMS

1. A compound of formula (I)

5

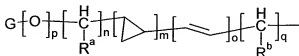


wherein

- 10 R¹ and R² independently represent a monocyclic or polycyclic heteroaryl group optionally substituted by one or more substituents selected from the group consisting of halogen atoms, straight or branched, optionally substituted lower alkyl, cycloalkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, -SH, straight or branched optionally substituted lower alkylthio, cyano, -NR'R'', -CO₂R', wherein R' and R'' each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R'' together with the nitrogen atom to which they are attached form a cyclic group;

20 R³ represents a group selected from -COR⁴, -CON(R⁴)R⁵, -COOR⁴ and -R⁴ wherein R⁴ represents a group selected from:

- hydrogen atoms,
 - a straight or branched lower alkyl group which is optionally substituted by one or more halogen atoms or by one or more cycloalkyl, hydroxy, lower alkoxy, lower alkylthio, amino, mono- or dialkylamino, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl and nitrile groups;
 - a group of formula:
- 25



30

wherein:

m, o and p are independently 0 or 1;

n and q are independently selected from integers from 0 to 6;

R^a and R^b are independently a hydrogen atom or a lower alkyl group;

G is a group selected from cycloalkyl, aryl or heteroaryl groups which are optionally substituted by one or more halogen atoms or by one or more lower alkyl, cycloalkyl, lower haloalkyl, hydroxy, lower alkoxy, lower alkylthio, amino, mono- or dialkylamino, hydroxyalkyl, alkoxyalkyl, hydroxycarbonyl, alkoxycarbonyl and nitrile groups;

and R⁵ represents a hydrogen atom or a lower alkyl, cycloalkyl or benzyl group; or

R⁴ and R⁵ together with the nitrogen atom to which they are attached form a saturated or unsaturated ring which is optionally substituted by one or more lower alkyl, cycloalkyl or benzyl groups;

or pharmaceutically acceptable salts thereof;

with the proviso that the compound is not 2,6-dipyridin-4-ylpyrimidin-4-amine.

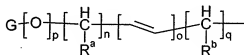
2. A compound according to claim 1 wherein R¹ represents a monocyclic heteroaryl group selected from the group consisting of furyl, thienyl, thiazolyl, oxazolyl, pirazinyl, pirazolyl, piridaziny, imidazolyl, triazolyl, pirimidiny and pyridyl groups which groups are optionally substituted by one or more substituents selected from the group consisting of halogen atoms and straight or branched, optionally substituted lower alkyl.
3. A compound according to claim 2 wherein R¹ represents a monocyclic heteroaryl group selected from the group consisting of furyl, thienyl, pirazolyl, triazolyl, thiazolyl and pyridyl groups which groups are optionally substituted by one or more substituents selected from the group consisting of halogen atoms and straight or branched, optionally substituted lower alkyl.
4. A compound according to any preceding claim wherein R² represents a monocyclic heteroaryl group selected from the group consisting of pirazolyl, furyl, thiazolyl, oxazolyl, pyridyl, pirimidiny, pirazinyl, piridaziny, thienyl, imidazolyl and triazolyl groups which groups are optionally substituted by one or more substituents selected from the group consisting of halogen atoms and straight or branched, optionally substituted lower alkyl.

5. A compound according to claim 4 wherein R^2 represents a monocyclic heteroaryl group selected from the group consisting of pirazolyl, furyl, thiazolyl, pyridyl, thienyl and triazolyl groups which groups are optionally substituted by one or more substituents selected from the group consisting of halogen atoms and straight or branched, optionally substituted lower alkyl.

6. A compound according to any preceding claim wherein R^4 represents a group selected from:

10

- hydrogen atoms,
- a straight or branched lower alkyl group which is optionally substituted by one or more halogen atoms;
- a group of formula:



15

wherein:

o and p are independently 0 or 1;

n and q are independently selected from integers from 0 to 6;

R^a and R^b are independently a hydrogen atom or a lower alkyl group;

- 20 G is a group selected from cycloalkyl, aryl or heteroaryl groups which are optionally substituted by one or more halogen atoms or by one or more lower alkoxy groups;

and R^5 represents a hydrogen atom.

- 25 7. A compound according to any preceding claim wherein R^4 represents a group selected from: .

- hydrogen atoms,
- a straight or branched lower alkyl group which is optionally substituted by one or more halogen atoms;
- a group selected from cycloalkylalkyl, phenylalkyl, heteroarylalkyl, phenoxyalkyl and heteroaryloxyalkyl groups which groups are optionally substituted by one or more halogen atoms or by one or more lower alkoxy groups;

30

and R⁵ represents a hydrogen atom.

8. A compound according to any preceding claim wherein R¹ is a 2-furyl group and R² is a pirazolyl group which is optionally substituted by one or more lower alkyl groups.
- 5
9. A compound according to claim 1 which is one of:

2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide
10 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]isobutyramide
N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]tertbutyramide
Cyclopropanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide
Cyclobutanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide
15 Cyclohexanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amide
3-Cyclopentyl-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl] propionamide
N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)-acetamide
2-(3,4-Dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acetamide
N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenyl-propionamide
20 E-2-Phenylcyclopropanecarboxylic acid [2-(furan-2-yl)-6-(pyrazol-1-yl) pyrimidin-4-yl]amide
3,3,3-Trifluoro-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl] propionamide
3-(3,4-Dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-2-methyl-3-phenylpropionamide
25 N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenoxy-propionamide
N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl)-propionamide
N-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(pyridin-3-yl) acetamide
E-3-(3,4-Dimethoxyphenyl)-N-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]acrylamide
2-(Furan-2-yl)-6-(3,5-dimethylpyrazol-1-yl)pyrimidin-4-ylamine
30 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]acetamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl] propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl] isobutyramide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl] tertbutyramide
Cyclopropanecarboxylic acid [6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]amide
35

- 3-Cyclopentyl-N-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide
- 5 2-(3,4-Dimethoxyphenyl)-*N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]acetamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenyl propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide
- 10 3-(3,4-Dimethoxyphenyl)-*N*-[6-(3,5-dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)pyrimidin-4-yl]-3-phenoxy propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)-pyrimidin-4-yl]-2-(pyridin-3-yl)acetamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(furan-2-yl)-pyrimidin-4-yl]-2-(pyridin-3-yl)propionamide
- 15 2-(Furan-2-yl)-6-(4-methylpyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(Furan-2-yl)-6-(4-methylpyrazol-1-yl)-pyrimidin-4-yl] propionamide
2-(Furan-2-yl)-6-(3-methylpyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(Furan-2-yl)-6-(3-methylpyrazol-1-yl)-pyrimidin-4-yl] propionamide
2-(Furan-2-yl)-6-(3-trifluoromethylpyrazol-1-yl)pyrimidin-4-ylamine
- 20 *N*-[2-(Furan-2-yl)-6-(3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl] propionamide
2-(Furan-2-yl)-6-(5-methyl-3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl amine
N-[2-(Furan-2-yl)-6-(5-methyl-3-trifluoromethylpyrazol-1-yl)pyrimidin-4-yl]propionamide
2-(Furan-2-yl)-6-[[1,2,4]triazol-1-yl]pyrimidin-4-ylamine
- 25 *N*-[2-(Furan-2-yl)-6-[[1,2,4]triazol-1-yl)pyrimidin-4-yl]acetamide
N-[2-(Furan-2-yl)-6-[[1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide
3,3,3-Trifluoro-*N*-[2-(furan-2-yl)-6-[[1,2,4]triazol-1-yl)pyrimidin-4-yl]-propionamide
2-(5-Bromofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(5-Bromofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
- 30 2-(5-Chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(5-Chlorofuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
2-(5-Methylfuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(5-Methylfuran-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
N-[2-(Furan-2-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide
- 35 2-(Furan-2-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamide

- 6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-ylamine
N-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]acetamide
N-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]propionamide
3-Cyclopentyl-N-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
5 3-Phenyl-N-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
3,3,3-Trifluoro-N-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
3-(3,4-Dimethoxyphenyl)-N-[6-(pyrazol-1-yl)-2-(thiophen-2-yl) pyrimidin-4-yl]propionamide
3-Phenoxy-N-[6-(pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
10 N-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-2-(pyridin-3-yl) acetamide
N-[6-(Pyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-3-(pyridin-3-yl) propionamide
E-3-(3,4-Dimethoxyphenyl)-N-[6-(pyrazol-1-yl)-2-(thiophen-2-yl) pyrimidin-4-yl]acrylamide
6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-ylamine
15 N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] acetamide
N-[6-(3,5-dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl] propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(thiophen-2-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide
2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine
20 N-[2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]acetamide
N-[2-(Thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide
3,3,3-Trifluoro-N-[2-(thiophen-2-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide
N-[2-(3-Methylthiophen-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl] propionamide
6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-ylamine
25 N-[6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]acetamide
N-[6-(Furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
3,3,3-Trifluoro-N-[6-(furan-2-yl)-2-(pyrazol-1-yl)pyrimidin-4-yl] propionamide
2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-ylamine
N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-yl] propionamide
30 N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(furan-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide
6-(Furan-2-yl)-2-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine
N-[6-(Furan-2-yl)-2-([1,2,4]triazol-1-yl)pyrimidin-4-yl]propionamide
2-(Pyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-ylamine
35 N-[2-(Pyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]propionamide

- 2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-ylamine
N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl] propionamide
N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide.
- 5 2-(Pyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamine
N-[2-(Pyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]propionamide
2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-ylamine
N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl] propionamide
N-[2-(3,5-Dimethylpyrazol-1-yl)-6-(pyridin-3-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)acetamide
- 10 2-(Pyrazol-1-yl)-6-(pyridin-4-yl)pyrimidin-4-ylamine
N-[2-(Pyrazol-1-yl)-6-(pyridin-4-yl)pyrimidin-4-yl]propionamide
6-(Furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-ylamine
N-[6-(Furan-2-yl)-2-(pyridin-2-yl)pyrimidin-4-yl]propionamide
- 15 2-(3-Methylpyridin-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-ylamine
N-[2-(3-methylpyridin-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]propionamide
6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine
N-[6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]acetamide
N-[6-(Pyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide
- 20 6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl] acetamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl] propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]-3,3,3-trifluoropropionamide
- 25 2-(Pyridin-3-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-ylamine
3,3,3-Trifluoro-N-[2-(pyridin-3-yl)-6-([1,2,4]triazol-1-yl)pyrimidin-4-yl] propionamide
6-(Furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-ylamine
N-[6-(Furan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-yl]propionamide
N-[6-(3,5-Dimethylpyrazol-1-yl)-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide
- 30 6-(3,5-dimethylpyrazol-1-yl)-2-(pyridin-4-yl)pyrimidin-4-ylamine
6-(Furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-ylamine
N-[6-(Furan-2-yl)-2-(pyridin-4-yl)pyrimidin-4-yl]propionamide
6-(Furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-ylamine
N-[6-(Furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-yl]propionamide
- 35 2-(4-Fluorophenyl)-N-[6-(furan-2-yl)-2-(thiazol-2-yl)pyrimidin-4-yl] acetamide

- N-(Cyclopropylmethyl)-2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-amine
(2R)-2-[[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]propan-1-ol
3-[[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]amino]propan-1-ol
N-[2-(2-Furyl)-6-(pyrazol-1-yl)pyrimidin-4-yl]ethane-1,2-diamine
- 5 2-(2-Furyl)-N-[2-(4-methoxyphenyl)ethyl]-6-(pyrazol-1-yl)pyrimidin-4-amine
N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(2-furyl)-6-(pyrazol-1-yl)pyrimidin-4-amine
2-(2-Furyl)-6-(pyrazol-1-yl)-N-[2-(pyridin-2-yl)ethyl]pyrimidin-4-amine
2-(2-Furyl)-6-(pyrazol-1-yl)-N-[2-(pyridin-3-yl)ethyl]pyrimidin-4-amine
2-(2-Furyl)-N-(3-phenylpropyl)-6-(pyrazol-1-yl)pyrimidin-4-amine
- 10 2-(2-Furyl)-N-[3-(imidazol-1-yl)propyl]-6-(pyrazol-1-yl)pyrimidin-4-amine
N-(Cyclopropylmethyl)-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
(2R)-2-[[6-(Pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amino]propan-1-ol
3-[[6-(Pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amino]propan-1-ol
N-(2-Aminoethyl)-N-[6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-yl]amine
- 15 N-[2-(4-Methoxyphenyl)ethyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
N-[2-(3,4-Dimethoxyphenyl)ethyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
6-(Pyrazol-1-yl)-N-[2-(pyridin-2-yl)ethyl]-2-(thien-2-yl)pyrimidin-4-amine
6-(Pyrazol-1-yl)-N-[2-(pyridin-3-yl)ethyl]-2-(thien-2-yl)pyrimidin-4-amine
N-(3-Phenylpropyl)-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
- 20 N-[3-(Imidazol-1-yl)propyl]-6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-amine
Ethyl 6-(pyrazol-1-yl)-2-(thien-2-yl)pyrimidin-4-ylcarbamate
1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(2-phenyl-cyclopropyl)urea
1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-propylurea
1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-isopropylurea
- 25 1-Cyclopentyl-3-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]urea
1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-(4-methoxy-phenyl)urea
1-[2-(Furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]-3-phenethylurea
1-Benzyl-3-[2-(furan-2-yl)-6-(pyrazol-1-yl)pyrimidin-4-yl]urea
- 30 10. A compound according to any one of claims 1 to 9 for use in the treatment of a pathological condition or disease susceptible to amelioration by antagonism of an adenosine receptor.
11. A compound according to claim 10 for use in the treatment of a pathological
- 35 condition or disease wherein the pathological condition or disease is ischemia,

supraventricular arrhythmias, acute renal failure, myocardial reperfusion injury, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, other autoimmune diseases, inflammatory bowel diseases, asthma, diabetes mellitus, obesity, Parkinson disease, Huntington's disease, dystonias such as restless leg syndrome, dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs or sleep disorders

5

10

12. A compound according to any one of claims 1 to 9 for use in the treatment of a pathological condition or disease susceptible to amelioration by antagonism of the adenosine A_{2A} receptor

15

13. A compound according to claim 12 for use in the treatment of a pathological condition or disease wherein the pathological condition or disease is ischemia, supraventricular arrhythmias, Parkinson disease, Huntington's disease, dystonias such as restless leg syndrome, dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs or sleep disorders.

20

14. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 9 mixed with a pharmaceutically acceptable diluent or carrier.

25

15. Use of a compound as defined in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible of being improved by antagonism of the adenosine receptors.

30

16. Use of a compound according to claim 15 wherein the pathological condition or disease is ischemia, supraventricular arrhythmias, acute renal failure, myocardial reperfusion injury, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, other autoimmune diseases, inflammatory bowel diseases, asthma, diabetes mellitus, obesity, Parkinson disease, Huntington's disease, dystonias such as restless leg syndrome, dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs or sleep disorders

35

17. Use of a compound as defined in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible of being improved by antagonism of the A_{2A} adenosine receptor.

18. Use according to claim 17, wherein the pathological condition or disease is ischemia, supraventricular arrhythmias, Parkinson disease, Huntington's disease, dystonias such as restless leg syndrome, dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs or sleep disorders.
19. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by antagonism of an adenosine receptor, which comprises administering to said subject an effective amount of a compound as defined in any one of claims 1 to 9.
20. A method according to claim 19 wherein the pathological condition or disease is ischemia, supraventricular arrhythmias, acute renal failure, myocardial reperfusion injury, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, other autoimmune diseases, inflammatory bowel diseases, asthma, diabetes mellitus, obesity, Parkinson disease, Huntington's disease, dystonias such as restless leg syndrome, dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs or sleep disorders.
21. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by antagonism of the A_{2A} adenosine receptor, which comprises administering to said subject an effective amount of a compound as defined in any one of claims 1 to 9
22. A method according to claim 21 wherein the pathological condition or disease is ischemia, supraventricular arrhythmias, Parkinson disease, Huntington's disease, dystonias such as restless leg syndrome, dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs or sleep disorders
23. A combination product comprising a compound according to any one of claims 1 to 9; and another compound selected from (a) L-DOPA, (b) dopamine antagonists, (c) inhibitors of dopamine decarboxylase (d) catechol-O-methyltransferase inhibitors and (e) inhibitors of monoamine oxidase for simultaneous, separate or sequential use